Appeal Nos. 2013-1454, -1484

IN THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

PROMEGA CORPORATION,

Plaintiff-Cross-Appellant,

v.

APPLIED BIOSYSTEMS, LLC,
LIFE TECHNOLOGIES CORPORATION, and CALIFORNIA INSTITUTE OF TECHNOLOGY,

Defendants-Appellants.

Appeals from the United States District Court
for the Northern District of Illinois,
Case No. 13-CV-2333,
Judge Richard A. Posner.

OPENING BRIEF FOR DEFENDANTS-APPELLANTS

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CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants Life Technologies Corporation, Applied Biosystems, LLC, and California Institute of Technology certifies as follows:

1. The full name of every party or amicus represented by us is:

   Applied Biosystems, LLC
   Life Technologies Corporation
   California Institute of Technology

2. The name of the real party in interest represented by us is:

   Applied Biosystems, LLC
   Life Technologies Corporation
   California Institute of Technology

3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   Formerly known as Invitrogen Corporation and traded under the symbol "IVGN," Life Technologies Corporation is a publicly held corporation and is now traded under the symbol "LIFE." Applied Biosystems, LLC is a wholly owned subsidiary of Life Technologies Corporation. When it was formerly part of Applera Corporation, Applied Biosystems was traded under the symbol "ABI."

4. The names of all law firms and the partners or associates that appeared for the parties now represented by us in the trial court or are expected to appear in this Court are:

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STATEMENT OF RELATED CASES

In May 2010, Promega Corporation ("Promega") filed a complaint in the Western District of Wisconsin alleging that Life Technologies Corporation ("Life"), Applied Biosystems, LLC ("Applied Biosystems"), and Invitrogen IP Holdings, Inc. infringed five patents. The appeal is pending in this Court. *Promega Corp. v. Life Tech.*, Appeal Nos. 2013-1011, -1029, -1376. This appeal (No. 2013-1454) involves a different patent, but the same 2006 Cross License at issue in the other pending appeal.

Counsel knows of no other cases pending in this Court or any other court that may directly affect, or be directly affected by, this Court's decision in this appeal.

PRELIMINARY STATEMENT

The patent-in-suit, U.S. Reissue Patent No. 43,096 ("the '096 patent"), covers an important innovation in DNA analysis. The invention of the '096 patent allows scientists to use multiple different fluorescent tags to label and differentiate between multiple pieces of DNA like never before. Developed in the early 1980s, the invention sprang from a pioneering collaboration between California Institute of Technology ("Caltech")[1] and Applied Biosystems that developed radioactivity-

[1] Caltech is the assignee-of-record for the '096 patent and shares rights to the patent with Applied Biosystems pursuant to an agreement between the two companies. Life and its subsidiaries, including Applied Biosystems, became the

free automated DNA sequencing. The inventions produced by this project ultimately enabled successful completion of the Human Genome Project. The district court properly recognized the importance of the '096 patent, characterizing it as "a breakthrough in biochemistry." A36.

Promega uses the invention in its DNA analysis products including to analyze crime scene samples, determine paternity, and authenticate cell lines in research laboratories. After claim construction, Promega conceded infringement.

In 2006 Promega licensed this invention, agreeing to pay a 2% royalty in the field of genetic identity analysis, with no license rights outside that field. This lawsuit arose when the '096 patent reissued and Promega refused to pay royalties under that license and also refused to stop selling outside its field of use.

After the completion of expert discovery and summary judgment motions were filed, the case was transferred from Wisconsin to Seventh Circuit Judge Richard Posner, sitting in Chicago. After the transfer, the district court welcomed a second round of summary judgment motions. At this stage the district court introduced a host of its own theories and a new defense altogether (double-patenting) that Promega had not even raised. As shown in this brief, by invalidating the '096 patent on summary judgment on its own theories, the district

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exclusive licensee of the '096 patent on October 30, 2012. A1466. Appellants Applied Biosystems, Life, and Caltech are collectively referred to herein as "Life/Caltech."

court improperly cast aside the clear and convincing burden of proof, formulated technical positions that conflicted with the views of both sides' experts, engaged in improper fact-finding and violated legal rules barring the use of the inventors own work as prior art.

JURISDICTIONAL STATEMENT

The district court had jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). Life/Caltech filed a timely appeal from the district court's final judgment on June 17, 2013, six days after entry of judgment. A17880-83. Promega subsequently filed a notice of appeal (No. 2013-1484), which was consolidated with this appeal. Jurisdiction in this Court is proper pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUES PRESENTED

1. Did the district court err by invalidating on summary judgment Claim 62 (and its dependents) and 66 for inherent anticipation based on Smith '800 under 35 U.S.C. §102(e)?

2. Did the district court err by invalidating on summary judgment Claim 62 (and its dependents) and Claim 66 for obviousness-type double-patenting based on Smith '800?

3. Did the district court err by invalidating on summary judgment Claim 67 as obvious?

4. Did the district court err by invalidating on summary judgment Claim 62 (and its dependents) for lack of written description?

5. Did the district court err by excluding the opinion of Life/Caltech's damages expert?

STATEMENT OF THE CASE

I. PROCEEDINGS IN THE WISCONSIN COURT

This case stems from the parties' 2006 Cross License. A541-63. In that license, Promega agreed that it would pay royalties for its use of the '096 patent when it reissued. On January 10, 2012, the Patent Office reissued the '096 patent after nearly a decade of examination. That same month, to avoid paying the royalties it agreed to pay, Promega filed a declaratory judgment complaint in the Western District of Wisconsin seeking to invalidate the reissued patent. A330 ¶ 1.

The operative complaint is the Fourth Amended Complaint. A1425-37. It seeks a declaration that the '096 patent is invalid, unenforceable for prosecution laches, and/or not infringed by Promega. *Id.* Life/Caltech counterclaimed against Promega for infringement of the '096 patent.[2] A1474-80 ¶¶ 62-90. Life/Caltech also sought relief for Promega's breach of the 2006 Cross License in failing to pay the agreed-upon royalties for its use of the '096 patent. A1480 ¶¶ 91-96.

On February 19, 2013, pursuant to the governing case management order,

[2] Specifically, Life/Caltech asserted the following claims against Promega: 62, 63, 65, 66, 67, 70, 74, 80, 86, 92, and 98. A6542-46.

the parties filed summary judgment motions based upon their contentions and the expert reports they had exchanged. A2293-94, 2342-442, 5772-74, 5775-842. Life/Caltech requested summary judgment of infringement[3] and that the '096 patent was entitled to the 1984 filing date of the original patent application.[4] A5801-41. Promega unsuccessfully cross-moved for summary judgment, arguing the '096 patent was invalid for reissue recapture and unenforceable. A2420-441.

While the initial summary judgment motions were pending, the case was transferred to the Northern District of Illinois on March 11, 2013, to Seventh Circuit Judge Posner, sitting by designation. A21854.

II. PROCEEDINGS IN THE CHICAGO COURT

After a March 28, 2013 hearing, the district court, now presided over by Judge Posner, issued a claim construction order and summary judgment rulings. A27-42. The district court denied Promega's motion for summary judgment on its defenses of reissue recapture and prosecution laches, and held that Promega's use of the PowerPlex 16 HS System infringes claims 62, 63, and 66 of the '096 patent. A32-39. The district court further ruled that Promega breached the 2006 Cross

[3] Pursuant to Wisconsin practices and procedures, Life/Caltech's first summary judgment motion of infringement focused on a representative Promega product: the PowerPlex 16HS.

[4] Promega originally contended that the priority filing date of the '096 patent ought to be later than the original application filing in 1984 because of new material added in a continuation-in-part application filed in 1987. A10243-47.

License by failing to pay royalties. A41-42. The district court recognized the work of the inventors to be "a major DNA invention." A40. Finally, the district court denied summary judgment regarding whether the claims deserved the 1984 filing date, finding that there were disputed facts. A39-41.

On April 19, 2013, the district court allowed the parties to supplement their expert reports by May 1, 2013 to address: (a) validity under section 112, and (b) the implications of the district court's constructions of the term "specifically hybridized" in the preamble of claim 62. A43-44.

The parties filed *Daubert* motions to exclude experts on May 15, 2013. A13177-211, 13212-28, 13275-95, 13409-26, 13468-517, 13518-46. The district court held *Daubert* hearings on May 22-24, 2013, examining all the experts. A48,

On May 27, 2013, the district court issued a *Daubert* order regarding the parties' experts. Among other rulings, the district court precluded Life/Caltech's damages expert Greene from testifying regarding a reasonable royalty rate. A48-55.

The district court subsequently ordered a second round of summary judgment briefing, in which Life/Caltech moved that: (1) all Promega's products infringe, (2) Promega is liable for indirect infringement, (3) Promega is liable for extraterritorial infringement, (4) Promega's invalidity and obviousness defenses fail as a matter of law, and (5) claim 67 of the '096 patent is valid under 35 U.S.C.

§112. A14645-708.

Promega cross-moved for summary judgment that all asserted claims were invalid under a combination of theories: (1) as anticipated by U.S. Patent No. 5,118, 800 ("Smith '800"), (2) obvious in light of Smith '800 combined with the general knowledge in the art, (3) obvious in light of U.S. Patent No. 4,948,882 ("Ruth '882") combined with the general knowledge in the art, and (4) for failure to meet the written description and enablement requirements. A14312-15, 14316-71.

In its opposition brief, Promega conceded direct and indirect infringement of all asserted claims for each accused product, and Promega confirmed that concession in open court. A16424-25; A18177-78 at 239:23-240:15.

On June 5, 2013, the district court *sua sponte* ordered the parties to submit, by the following evening, simultaneous briefs addressing whether the '096 patent is invalid for obviousness-type double-patenting based on Smith '800. The district court raised this issue itself even though Promega had never raised double-patenting as a defense—not in its pleadings, its invalidity contentions, its numerous expert reports, nor in any of its summary judgment motions. A59.

In response to the district court's order, in less than 36 hours Life/Caltech submitted an expert declaration establishing the significant differences between the claims of Smith '800 and the claims of the '096 patent; thus rebutting the district

court's obviousness type double-patenting theory. A17248-72. In contrast, Promega submitted no evidence supporting obviousness-type double-patenting, and, indeed, even failed to separately plead it as required. *See, e.g.*, *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991); *Engineered Prods. Co. v. Donaldson Co., Inc.*, 147 F. App'x 979, 987-88 (Fed. Cir. 2005).

The next day, June 7, only three days after it had first introduced the defense, the district court held a summary judgment hearing. On June 12, 2013, the district court granted summary judgment in Promega's favor that: (1) claims 62 (and its dependents) and claim 66 of the '096 patent are invalid based on inherent anticipation by Smith '800, (2) claims 62 (and its dependents) and claim 66 are invalid due to obviousness-type double-patenting, (3) claim 67 is invalid as obvious based on a combination of references not asserted by Promega, and (4) claim 62 (and its dependents) are invalid for lack of written description. A60-79. Judgment was subsequently entered on June 13, 2013. A80.

STATEMENT OF FACTS

I. THE INVENTORS DEVELOP GROUNDBREAKING DNA TECHNOLOGY

In the early 1980s, scientists in Leroy Hood's laboratory at Caltech collaborated with scientists at startup Applied Biosystems to automate DNA sequencing. A19599 at 200:16-22. This development project "revolutionized molecular biology . . . [and] enabled the human genome project . . . probably the

most transformational big science project in all of biology." *Id.* The inventions arising out of this project, including those in the '096 patent, transformed DNA sequencing from a dangerous, laborious and inefficient process requiring radioactive labels to a much safer, faster, and more efficient system employing fluorescent labels.

As this Court knows, DNA is the molecule that contains the genetic code for living organisms. *See, e.g.*, *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08 n.4 (Fed. Cir. 1991). DNA is composed of a double helix and a series of four nucleic acids, Adenine, Thymine, Guanine and Cytosine—commonly referred to as A, T, G and C. When double-stranded DNA separates into two strands, each strand can be extended from only one of its ends. The extendable end of the strand is called the 3' end, while the other, non-extendable end is called the 5' end. An enzyme called polymerase performs the extension process.

The inventors worked on the chemistry of DNA labeling, methods of sequence analysis, and machines with computer processing to automate that analysis. From this broader project, the inventions of both Smith '800 and the '096 patent arose. A21103-04 at 48:20–49:8 ("[A] key aspect of the invention was how to—replace the then methodology for doing nucleic acid analysis . . . that involved the use of radioactive tags with tags that could be—monitored by spectroscopic means, and . . . [the inventors] collectively came up with the general approach of

using fluorophores as a way to substitute for the radioactive tags, and that . . . arose through a series of discussions . . . until we got to a scheme that we thought would work.").

The methods of DNA sequence analysis at the time had "serious drawbacks." A94 at 2:48-49. For example, radioactive labels were difficult to handle and required manual reading of the results. *Id*. at 2:55-65. Additionally, radioactive tags could only be used one at a time—there was no way to differentiate between different radioactive tags. A11611-12 ¶ 37.

The inventive solution of the '096 patent was twofold. First, the inventors discarded the radioactive tags in favor of multiple colors of fluorophores (*i.e.*, fluorescent tags). Second, the inventors placed these tags at the 5' end of oligonucleotides[5] so that the 3' end was available for extension unhindered -- and recognized that these large inorganic tags would not interfere with nucleic acid extension, even though the community feared this.

The inventors had another critical insight. They concluded that four distinct fluorescent labels could be used for genetic analyses to "multiplex." Such multiplexing greatly simplifies genetic analysis because more reactions can be combined and run simultaneously. For example, it eliminates the need to perform four separate sequencing reactions (one for each type base instead allowing all four

[5] "An oligonucleotide is a short polymer consisting of a linear sequence of four nucleotides in a defined order." *See* A95 at 3:6-7.

reactions to occur in a single tube using four different colors to differentiate among the four base types). *See, e.g.*, A96 at 6:14-18.

The inventors recognized that the labeled oligonucleotides they created were "powerful tools" that would have "numerous applications" including as probes and primers. *See, e.g.*, A95 at 3:54-62. The '096 patent teaches that oligonucleotides may be used for fragment analysis in addition to sequence identification. A96 at 5:14-15.

II. THE '096 PATENT

Caltech filed its original application on January 16, 1984. The application named as inventors Caltech's Lloyd Smith, Leroy Hood, Michael Hunkapiller and Timothy Hunkapiller. A8299-300 ¶ 101. Co-inventor and Applied Biosystems employee Charles Connell was added during prosecution. A21434-35 at 141:20-142:7. On March 13, 2001, the Patent Office issued U.S. Patent No. 6,200,748 (the "'748 patent") to Caltech.

On March 13, 2003, Caltech filed a reissue application within two years of the issue date of the '748 patent. On January 10, 2012, the Patent Office reissued the '096 patent.

The asserted independent claims of the '096 patent are:

> 62. A method of nucleic acid sequence analysis,
>
> comprising extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled

extension product,

wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA,

and wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase

66. A mixture

comprising a polymerase and a duplex,

wherein the duplex comprises an oligonucleotide specifically hybridized to a complementary strand of DNA,

wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

67. A composition

comprising four sets of oligonucleotides,

wherein oligonucleotides of each of the four sets are distinguishably labeled with a different type of fluorophore from the oligonucleotides of the other three sets.

A100 at 14:22-29, 48-56.

III. THE PATENT OFFICE CONSIDERED ALL THE CITED ART

During examination, the Patent Office considered, and issued the patent over, all the art relied upon by the district court for invalidity, including: (a) Smith '800, (b) Ruth '882, and (c) and an October 1982 research abstract of a lecture presented by Masayuki Tsuchiya, Yuzuru Hushimi, and Yasunori Kinishita ("Tsuchiya").

Smith '800: Smith '800 issued on June 2, 1992, and claims priority to

December 20, 1983. A119. Smith '800 is assigned to Caltech. *Id.* Smith '800 identifies the application from which the '096 patent arose as a pre-existing and separate invention of a different inventor group and acknowledges that work. A121 at 3:64-68.

All claims of Smith '800 relate to specific chemical formulae for oligonucleotide compounds that contain an amino group attached to the sugar moiety of nucleotide subunits, which serves as a linker. A144-45. According to unrebutted expert testimony, the claims do not cover fluorescent labels. A17268-72.

During examination of the '096 patent, to overcome a rejection, Caltech submitted a Rule 131 declaration from Lloyd Smith swearing that fluorescent dye labeled oligonucleotides were used in DNA sequencing reactions before the filing date of the application that led to Smith '800. A4497-98. The Patent Office accepted that declaration.

Ruth '882: Ruth '882 issued on August 14, 1990 to Ruth, one of Promega's retained experts. Ruth '882 claims a priority date of February 22, 1983. A146.

The claims of Ruth '882 are representative of the specification and relate to the structure of modified mononucleotides useful (according to the claims) as an intermediate in a chemical reaction. Ruth '882 describes the inclusion of labeled monomers in an oligonucleotide. A148. As explained by Life/Caltech's expert,

Ruth '882 expresses concern that modification of oligonucleotides might disrupt the workings of the enzymes such as those needed to extend an oligonucleotide along a complementary strand. A11663 at ¶ 129 (citing A147 at 2:5-8). *See also* A148-49 at 4:66-5:16.

Ruth '882 was cited on the face of the '096 patent, indicating that the Patent Office considered the reference during examination and determined the '096 patent was patentable over it. A81.

Tsuchiya: Tsuchiya is a summary of a master's thesis prepared in 1983 by a student at Saitama University. The Patent Office fully considered this reference.

Tsuchiya discusses the use of a well-known chemical reaction to modify a portion of a DNA molecule called adenosine into "ethenoadenosine," a weakly fluorescent molecule. A17188. Tsuchiya claims to have used the reaction to modify existing DNA molecules into fluorescent ones in three different ways: (1) modifying the adenosines in a pre-existing single strand of DNA; (2) cutting double-stranded DNA and modifying the two terminal adenosines; and (3) adding a modified version of adenosine to the 3' terminus of the double-stranded DNA. *Id.*

Importantly, each of these three methods results in the ***same*** fluorescent molecule: ethenoadenosine, and each of these methods was done separately. *Id*. Thus, Tsuchiya discusses only the preparation of a single nucleotide, with a single

fluorescent label, and does not provide any useful guidance to one of skill in the art about the use of multiple distinguishable fluorophores, or how a set of DNA labeled with four different fluorophores could be created. At most, the Tsuchiya material merely asks the question "if multi-color labeling is possible." *Id.*

IV. PROMEGA LICENSES THE '096 PATENT

In August 2006, while the reissue was pending, Promega and Applera (predecessor to Applied Biosystems) entered into the 2006 Cross License. The license is limited to the "Genetic Identity Field." A1509 ¶ 1.7. This covers "any analysis, based on the measurement of the length of a polynucleotide sequence containing a tandem repeat, of human genetic material" for certain purposes. A1509-10 ¶¶ 1.6, 1.11.

Promega agreed to pay royalties for its use of the reissue of the '748 patent in that limited field. A1512-13 ¶ 3.2.

SUMMARY OF THE ARGUMENT

The district court improperly treated the summary judgment process as an opportunity for it to impose its own views of the law, and of the technology and facts in lieu of a trial. Indeed, the district court committed pervasive error by pursuing its own invalidity theories—in almost every case theories that even the party alleging invalidity, Promega and its experts, did not embrace.

First, the district court invalidated a series of claims for anticipation based on its opinion that Smith '800 "expressly or inherently" disclosed those inventions under §102(e). A67. As an initial matter, Promega's experts never agreed with this conclusion given that numerous key elements of the invention are missing from that reference. Indeed, Life/Caltech ***and*** Promega's technical experts hold opinions that are irreconcilable with the speculative inherency theories posited by the district court. That is classic legal error, especially on summary judgment.

Even beyond the weakness of the district court's opinions on DNA technology, Smith '800 is not prior art at all. Smith '800 refers to the inventions made by the inventors of the '096 patent. It is legally improper to use the inventors own inventions against them even if their inventions are referenced in the patent application of "another." But that is exactly what happened here.

Second, the district court pursued an obviousness-type double-patenting theory that Promega did not plead, much less attempt to support. Promega did not assert obviousness-type double-patenting at all. When the district court introduced this defense (based on Smith '800), it allowed Life/Caltech only ***two days*** to try to develop expert testimony on this new defense and respond with legal analysis.

As it turns out, the district court did ***not*** discover a valid defense missed by the Patent Office and Promega—both had full incentive to identify all invalidity arguments. Obviousness-type double-patenting does not apply because it requires

the comparison of claims from an earlier patent to the later patent, but the claims of Smith '800 are very different. The district court does not dispute this, but instead attempts to expand the "limited exception" from *Lilly* to consider the specification of the earlier patent where it references the application of the '096 patent. But the *Lilly* exception is inapposite. The specification of the earlier patent *cannot* be used for obviousness-type double-patenting where, as here, the relevant portions state that they are describing the inventions of the later patent and do not purport to describe the claimed inventions of the earlier patent. That is explained in this Court's decision in *In re Kaplan*, 789 F.2d 1574 (Fed. Cir. 1986). The district court's double-patenting finding should be rejected.

Third, the district court granted summary judgment of obviousness of claim 67 by constructing its own combination of references. This was rife with problems. The district court used the '096 patent as a blueprint for impermissible hindsight analysis. It misconstrued and selectively quoted from references to support its theory. It ignored conflicting opinions of Life/Caltech ***and*** Promega's technical experts. And it engaged in fact-finding on summary judgment while at the same time ignoring strong evidence of objective indicia of non-obviousness.

Fourth, the district court wrongly found claim 62 (and its dependents) lacked written description. The district court's error stems from its misimpression that new products and applications for the invention are supposed to be described in the

patent itself. It should not be surprising that a groundbreaking invention is used in new applications. The realization of many new uses proves the power of the invention; it is not a basis to invalidate the patent.

Finally, the district court also wrongly abused its gatekeeper role when it totally struck the opinion of Life/Caltech's damages expert based on standards unsupported by precedent. The damages expert applied the well-accepted methodology of Georgia-Pacific to calculate a reasonable royalty.

STANDARD OF REVIEW

"To overcome th[e] presumption of validity, the party challenging a patent must prove facts supporting a determination of invalidity by clear and convincing evidence." *Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002) (citation omitted). On summary judgment, the Court views the evidence through the prism of the evidentiary standard of proof that would pertain at trial. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). All justifiable inferences are made in favor of the non-movant. *Schumer*, 308 F.3d at 1315. Where, as here, the Examiner considered the asserted prior art during patent prosecution, the burden to overcome the presumption of validity is "especially difficult." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

This Court reviews a grant of summary judgment *de novo*. *Move, Inc. v.*

Real Estate Alliance Ltd., 709 F.3d 1117, 1121 (Fed. Cir. 2013). Whether a reference qualifies as prior art is a legal question reviewed *de novo*. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1352 (Fed. Cir. 2003).

As this Court reviews this summary judgment record, it is worth keeping in mind the following guidance from the Seventh Circuit only weeks ago in *Pactiv Corp. v. Rupert*:

> If judges could decide suits without warning on the basis of considerations the litigants were not contesting, litigation would be even less manageable than it is already. Lawyers would need to submit evidence and legal arguments on issues that appeared to be irrelevant, on the off chance that the judge would second guess the parties' litigation strategies. That would produce delay, bloat, and expense. As a norm, waivers are forever. If a waived or forfeited issue is to come back to life, the revival must be preceded by notice. Litigants then safely can limit their submissions to the subjects genuinely in dispute.

__ F.3d __, No. 12-3704, 12-3804, 2013 WL 3944283, at *2 (7th Cir. Aug. 1, 2013).

Finally, decisions under *Daubert*, are reviewed under the law of the regional circuit. *Micro Chem., Inc. v. Lextron, Inc.*, 317 F.3d 1387, 1390-91 (Fed. Cir. 2003). In the Seventh Circuit, the decision to admit or exclude expert testimony is reviewed for abuse of discretion. *Lapsley v. Xtek, Inc.*, 689 F.3d 802, 809 (7th Cir. 2012). The Seventh Circuit will, however, review *de novo* the "district court's understanding and proper application of the multi-factor *Daubert* framework." *Id.*;

see Metavante Corp. v. Emigrant Sav. Bank, 619 F.3d 748, 760 (7th Cir. 2010) (applying *de novo* review).

ARGUMENT

I. IT WAS LEGAL ERROR TO USE SMITH '800 TO INVALIDATE NUMEROUS ASSERTED CLAIMS ON SUMMARY JUDGMENT

The district court ruled on summary judgment that Smith '800 is prior art that inherently or expressly anticipates independent claim 62 (and dependent claims) and claim 66 under §102(e). A64, 66-70. Smith '800 is not prior art and, even if it were, it does not anticipate either expressly or inherently. And it certainly does not do so as a matter of undisputed fact.

The Patent Office examiners were aware of Smith '800 and did not find it anticipates. Promega's invalidity experts were aware of Smith '800 and did not find that it anticipates. They were all correct. As demonstrated below, the district court committed two major legal errors in making a contrary finding, each error independently warranting reversal and elimination of Promega's anticipation defense.[6]

A. BECAUSE SMITH '800 IS NOT PRIOR ART, SUMMARY JUDGMENT WAS IMPROPER

Smith '800 is not prior art for two independent reasons. First, the district court relied on a portion of Smith '800 as supposed prior art that, on its face, is a

[6] There are no other anticipation allegations remaining in the case.

cross-reference to the pre-existing inventive work underlying the '096 patent itself. In other words, the inventors' own invention was wrongly used against them as supposed prior art merely because it was cross-referenced by another. Second, the district court ignored uncontested evidence accepted by the Patent Office that the invention of the '096 patent predates Smith '800. The district court improperly relied on the waiver doctrine to ignore the conclusive effect of that evidence on Smith '800's status as prior art under §102(e).

1. THE INVENTORS' OWN WORK IS NOT PROPERLY CITED AGAINST THEM UNDER §102(E)

Caltech filed the application and several continuations-in-part applications in a chain that led to Smith '800. Smith '800 claims priority to December 1983, one month prior to the application that led to the '096 patent. Smith is a named inventor of both patents. The disclosure relied upon by the district court in Smith '800 is not prior art because it merely reports on the invention of the '096 inventors. This does not qualify as §102(e) prior art under long-standing legal principles.

2. THE PORTION OF SMITH '800 RELIED UPON BY THE COURT IS A REFERENCE TO THE '096 PATENT

The district court relied upon statements in Smith '800 that reference the use of its linker chemistry for DNA sequencing. But this is simply a cross-reference to the '096 application. To be specific, Smith '800 acknowledges that its references

to DNA sequencing relate to the ***separate set of pre-existing inventions*** described in the '096 patent.

The district court relied upon Smith '800 because it "describes the use of these fluorescently tagged oligonucleotides in DNA sequencing: '[...] the synthesis of fluorescent-labeled oligonucleotides permits the automation of the DNA sequencing process' (3:64-68) and the labeled oligonucleotides 'are effective in DNA hybridization methods, as illustrated by their use as primers in DNA sequence analysis.' (5:51-55)." A66 (quoting Smith '800) (brackets added to show omission).

The district court, however, left out the passage most important to this issue. The district court omitted that Smith '800 states that the idea of sequencing with its chemistry invention was the pre-existing work of a different inventorship entity described in the '096 patent: "***As described in the assignees co-pending application for a DNA sequencing machine Ser. No. 570,973, filed Jan. 16, 1984)*** the synthesis of fluorescent labeled oligonucleotides permits the automation of the DNA sequencing process." A121 at 3:64-68[7]. The 570,973 application is the original application leading to the '096 patent. Thus, the district court was citing the '096 inventors' own work against them in its invalidity ruling as though

[7] Emphasis is supplied unless otherwise stated.

it were somehow the work of the Smith '800 inventors or part of their invention when it was a cross-reference.[8] *See id*.

3. AN INVENTOR'S PREEXISTING WORK CANNOT BE USED AS SECTION 102(E) PRIOR ART

Section 102(e) provides that a patent application is properly prior art under this section only insofar as it is the work of "another" *and* the application predates the invention date for the patent at issue. This requirement is not met because the disclosure relied upon by the district court in Smith '800 is the *non*-prior art, pre-existing work of the inventors of the '096 patent.

This Court's predecessor[9] addressed a similar situation in *Application of Blout*, 333 F.2d 928 (C.C.P.A. 1964). There, the Patent Office rejected the application of an inventorship team (Blout and Rogers) because one of the inventors (Rogers) had filed an earlier application that matured into a patent that it concluded was §102(e) prior art. The alleged Section 102(e) patent disclosed and claimed dye developers as Rogers' invention. But it also disclosed (but did not claim) the improvement of Blout and Rogers of an *insulated* dye developer. The Patent Office had relied on Rogers' disclosure of the Blout and Rogers

[8] The district court also quoted from column 5 of the Smith '800 patent. As admitted by Promega's expert, that too was the work of the co-inventors (*see, e.g.,* A11271-72), explaining that the column 5 subject matter was referring to and based on the '096's disclosure of primers for DNA sequencing).

[9] CCPA decisions are "binding precedent" for this Court. *South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (*en banc*).

improvement to show the Blout and Rogers application was anticipated. The CCPA held that this was error. The invention of Blout and Rogers disclosed in the earlier application was not the work of "another" and thus did not qualify as 102(e) prior art. *Id.* at 931.

In *Application of Land*, 368 F.2d 866 (C.C.P.A. 1966) this Court's predecessor set forth the applicable rules in detail. The Court explained that an individual inventor disclosing her own invention is likely to reference in her patent application a different and pre-existing invention that she created jointly with other inventors because such knowledge is already in her head:

> When the joint and sole inventions are related, as they are here, **inventor A commonly discloses the invention of A & B in the course of describing his sole invention and when he so describes the invention of A & B he is not disclosing "prior art" to the A & B invention**, even if he has legal status as "another."

Land, 368 F.2d at 879 (emphasis added).

The Court in *Land* further explained that, if an individual inventor is merely reporting on the work of a joint inventorship group with whom he has collaborated on a different invention, that reported work is not the *prior* work of another under §102(e) that could constitute prior art:

> When the 102(e) reference patentee got knowledge of the applicant's invention from him, as by being associated with him, or, as here, had knowledge of the joint applicants' invention by being one of them, and thereafter describes it, he necessarily files the application

> after the applicant's invention date and the patent as a "reference" does not evidence that the invention, when made, was already known to others.

Id.

The teaching of *Land* is pure logic. If the putative prior art patent is reporting on an invention of another that already occurred, it is impossible for the reporting on that prior invention to show that the invention was already known to others before it was invented.

Land addressed the seminal *Blout* decision. The CCPA explained that, when the alleged 102(e) reference describes the work of a related inventorship group, the disclosure of that related inventorship group's invention *absolutely cannot* be used to invalidate their patent:

> The true basis of our decision "that the Rogers patent is not properly a reference against Blout and Rogers" was that the evidence before us showed that the alleged anticipatory disclosure in the Rogers patent was a description of the Blout and Rogers joint invention, not the invention of another. In that sense only Rogers was not "another," but as a patentee, of course, he was. However **the disclosure relied on was not his invention, or that of a third party as in Milburn, but the *applicants' own invention which, as against them, could not possibly be prior art.***

Land, 368 F.2d at 879 n.10 (emphasis added).

The CCPA faced like circumstances again in *Application of Mathews*, 408 F.2d 1393 (C.C.P.A. 1969). In *Mathews*, the alleged prior art was a patent to

Dewey. Dewey had disclosed the invention of his colleague Mathews in his application. After Dewey had filed his application, Mathews filed an application on his own invention. The Patent Office rejected Mathew's application based on Dewey's disclosure of Mathew's invention in his patent under Section 102(e) as a patent of "another." In view of the principle that an inventor's own work cannot invalidate under § 102(e) even if it is disclosed in the earlier filed patent of another, the CCPA reversed: "The Dewey disclosure relied on, being a disclosure of Mathews' own invention, does not establish lack of novelty of Mathews' claimed invention." 408 F.2d at 1396; *see also Application of Bulloch*, 604 F.2d 1362, 1366 (C.C.P.A. 1979) ("This disclosure to Kroll et al. by appellants regarding their prior invention, notwithstanding its publication in the Kroll patent, cannot be used subsequently as 'prior art' against appellants.")

As explained above, the disclosure of DNA sequencing in Smith '800 was a cross-reference to a different and preexisting invention of a different inventive entity covered by a different patent application (which matured into the '096 patent). Those DNA sequencing inventions, as a matter of logic, must have predated the December 1993 application describing chemistry inventions because that application describes them as already existing. Thus, under a straightforward application of the sound logic of *Land*, and applying the truism that an inventor's own work cannot invalidate its patent under 102(e) even if it is disclosed in an

earlier application of another, the disclosure of Smith '800 ***cannot*** be proof that the '096 inventions were invented by another before the '096 inventors invented it themselves.

4. THE '096 INVENTION IN FACT PREDATES SMITH '800 AND SMITH '800 THEREFORE CANNOT BE PRIOR ART UNDER 35 U.S.C. §102(e)

The Patent Office considered Smith '800 during the prosecution of the '096 patent. The examiner rejected the claims of the '096 patent under §102(e) as anticipated by U.S. Patent 4,849,513, which is in the same family as Smith '800 and likewise traces its priority to the December 1983 application. The file history for the '096 patent contains a Rule 131 declaration from Smith, declaring that the invention of the '096 patent occurred ***before*** the December 20, 1983 priority filing date of Smith '800 by attesting that the inventors had "conceived and reduced to practice oligonucleotide primers labeled with fluorescent dyes in the United States prior to December 20, 1983" and that "fluorescent dye labeled oligonucleotide primers were used in DNA sequencing reactions in the United States prior to December 20, 1983." A4497.

The Patent Office accepted the Rule 131 declaration, withdrew the 102(e) rejection, and allowed the claims. A4623. This Rule 131 declaration—the substance of which went unchallenged by Promega throughout the litigation—is an independent and sufficient basis for establishing that Smith '800 is not prior art.

5. THE DISTRICT COURT'S FINDING THAT SMITH '800 IS PRIOR ART DEPENDED ON AN IMPROPER "WAIVER" FINDING

The district court acknowledged in its summary judgment order that, if the date of invention for the '096 patent necessarily predated the December 1983 priority date of Smith '800, it would not be prior art. A64 ("the technology patented in the '096 patent may[10] have been invented before the '800 patent application was filed, which would prevent the '800 patent from being used as prior art to challenge the validity of the '096 patent").

Yet, the district court found that Life/Caltech waived the position that the cross-reference to the disclosure of DNA sequencing in the Smith '800 is a disclosure of the inventions in the '096 patent. This makes no sense. Smith '800 states that the use of the linker chemistry for DNA sequencing is the work of the '096 inventors. Why would the ability to identify that truth be waived? Because the Smith '800 application itself acknowledges that the inventions of the '096 patent already existed prior to the original Smith '800 filing and were invented by the '096 patent's inventors, the relied upon portions of that application cannot be prior art as a matter of sheer logic based solely on the face of the Smith '800 patent. The burden to prove that the requirements of §102(e) lie with Promega, and *Land* prevents Promega from meeting its burden. The doctrine of waiver

[10] There is no "maybe" about it. Smith '800 references the '096 application and invention so they must have existed before the application.

simply has no role to enforce a counter-factual outcome such as this.

In any event, there is nothing showing that Life/Caltech relinquished a known right to rely upon the fundamental logic of *Land* in response to an assertion that Smith '800 is §102(e) prior art. *See, e.g.*, *Coll. Sav. Bank v. Fla. Prepaid Postsecondary Educ. Expense Bd.*, 527 U.S. 666, 682 (1999). Nor is there such a basis as it relates to the factual proof that the '096 inventions predated December 1983 as set forth in the Smith declaration. According to the court, Life/Caltech "moved for summary judgment that the ***priority date*** is January 16, 1984 . . . [;] denied that there was any evidence of earlier date in its interrogatory responses; and failed to amend those responses in timely fashion." A64. This ruling was incorrect. It confuses the issue of priority date under 35 U.S.C. §120 and whether a reference is prior art under §102(e), and also improperly ignores uncontroverted facts that were, and had always been, in the public record.

There was no waiver because Life/Caltech properly responded to Promega's invalidity challenge. Promega's invalidity position was that the '096 patent was entitled to a priority date no earlier than 1987. In response, Life/Caltech sought summary judgment to establish entitlement to a priority date of January 1984 based upon the adequacy of the original disclosure under 35 U.S.C. §120. A5834-38. This was not an argument that the ***invention*** date should be set as January 1984.

The district court's reliance on its decision to strike Life/Caltech's

interrogatory response was similarly misplaced. To impose the sanction of precluding Life/Caltech from showing that Smith '800 merely reports on the '096 patent was an abuse of discretion. *Sherrod v. Lingle*, 223 F.3d 605, 612 (7th Cir. 2000) (discovery sanction requires showing that challenged conduct was both "unjustified and harmful"). The sanction is inapposite because the evidence of an early conception date is a different question than whether the disclosures in Smith '800 are truly of "another" or simply the inventors' disclosure of their own invention. Moreover, even if the timing of the disclosure of an earlier invention date was unjustified, it was *not* harmful. Promega simply cannot meet its burden of showing that the disclosures of the '096 DNA sequencing inventions in Smith '800 are of "another." An inventor's own work cannot invalidate its patent under 102(e) even if it is disclosed in an earlier application of another and that's conclusive independent of the content or timing of the discovery response.

B. SMITH '800 DOES NOT ANTICIPATE THE '096 PATENT EITHER EXPLICITLY OR INHERENTLY

Even if Smith '800 were somehow properly considered prior art, the district court erred in its anticipation analysis, both by ignoring Promega's failure of proof of anticipation, and then by conducting its own lay fact-finding to support arguments never advanced by Promega.

1. PROMEGA FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE OF ANTICIPATION BY SMITH '800

An immediate red-flag is that neither of Promega's two invalidity experts were willing to opine that Smith '800 anticipated. A68 ("Promega's experts have not said that the '800 patent anticipates the '096 patent."); A19095 at 27:4-7 (admitting that his anticipation opinions were "based solely on the 1986 paper by Smith").[11]

There is good reason for this. Promega's experts were adamant that the problem conquered in the '096 patent was so challenging that even the 1984 application which directly discloses and claims the invention does not enable the claims and that Smith's landmark 1986 Science article does not do so. A10243-47.

Promega's technical expert Dr. Van Ness contends that the state of the art was so unready for the '096 inventions that the inventor's extensive disclosures were inadequate because they did not disclose four robust dyes, the disclosed oligonucleotides were "not long enough," and the disclosures did not explain sufficiently that the complementary DNA strands needed to be unique. *Id*.

Promega's other technical expert, Jerry Ruth, held the same view. Ruth testified that he did not even believe the 1986 Smith Paper enabled the invention of

[11] The court ignored Promega's experts by concluding that expert witnesses are not "required . . . to offer legal conclusions" such as whether Smith '800 anticipates. A68. This is wrong because anticipation is a question of fact. *z4 Techs., Inc. v. Microsoft Corp.*, 507 F.3d 1340, 1347 (Fed. Cir. 2007).

the ‘096 patent:

> Q. Do you have any opinion regarding whether the Smith 1986 paper enables the invention of the ‘096 patent?
>
> A. ***Well, I don’t—I don’t believe it enables it in a practical sense***. I think it pretty much communicates the concept. But, for example, there’s very little—if you don’t mind me refreshing my memory here. ***There’s very little detail in making and labeling the oligonucleotides that are used as primers in the 1986 Smith reference. And using this as a stand-alone, I wouldn’t be able to replicate the work very precisely because of the lack of detail***.

A19097-98 at 37:20–38:12. (objection omitted). Given Promega’s litigation approach and expert opinion that the ‘096 patent claims were not enabled by even the full ‘096 disclosure, it was error for the district court to ignore that position and assume that the passing reference to sequencing (*i.e.*, the bare cross-reference to the ‘096 patent’s invention) in Smith ‘800 somehow rendered Smith ‘800 sufficiently enabled to anticipate the ‘096 patent claims.

Promega was required to present clear and convincing evidence that Smith ‘800 patent anticipated given the technical subject matter, rather than just benefiting from the court’s opinion regarding the technology—and yet its evidence actually ***disproved*** **an enabling** anticipation as explained above. *See, e.g.*, *Koito Mfg. Co. v. Turn-Key Tech, LLC*, 381 F.3d 1142, 1151 (Fed. Cir. 2004) (anticipation requires “testimony or other evidence that would demonstrate to the jury how that reference met the limitations of the [patent claims] . . . or how the

reference enabled one of ordinary skill in the art to practice the claimed invention"); *Finisar Corp. v. DirecTV Grp.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008); *see also Schumer*, 308 F.3d at 1315 ("Typically, testimony concerning anticipation must be testimony from one skilled in the art and must identify each claim element, state the witnesses' interpretation of the claim element, and explain in detail how each claim element is disclosed in the prior art reference."); *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1267 (Fed. Cir. 2008) (expert testimony required to establish anticipation and obviousness where subject matter is sufficiently complex to fall beyond the grasp of an ordinary layperson); *Aspex Eyewear, Inc. v. Concepts in Optics, Inc.*, 111 F. App'x 582, 588 (Fed. Cir. 2004) (party asserting invalidity had burden of asserting expert testimony as case was "not one of those rare cases where the invention is so simple that expert testimony is not required").

Not only was the district court's grant of summary judgment of anticipation substantively incorrect, by Promega's own evidence there is no anticipation as a matter of law.

2. THE DISTRICT COURT ERRONEOUSLY CONCLUDED THAT SMITH '800 INHERENTLY ANTICIPATES THE '096 PATENT

The district court started its inherency analysis by noting that Smith '800 expressly discloses an "oligonucleotide . . . covalently coupled to a fluorophore." The district court found many other limitations to be inherently disclosed. A66-68

(characterizing the invention of the '800 patent as "the linker arm" of an oligonucleotide and contending that "[e]ach of the additional elements of the claim is inherently present in the Sanger method"). In short, many of the limitations of the asserted claims are not expressly present and can at best only be found through inherency. A68.

But inherency cannot be established by probabilities or possibilities, as the "mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)) (emphasis in original). Instead, inherency requires clear and convincing evidence that the missing description is necessarily present—not probably or possibly present—in the prior art. *See Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295-97 (Fed. Cir. 2002) (vacating district court's grant of summary judgment that asserted claims were inherently anticipated).

Even though the district court's technical analysis conflicts directly from the testimony of all the experts, it cites no evidence, and in fact no evidence was presented, that the multitude of missing limitations were ***necessarily*** present in Smith '800. The district court relied on two passages in Smith '800 that refer to "automation of the DNA sequencing process" and the use of fluorescent oligonucleotides as "primers in DNA sequence analysis" (both of which are

references to the '096 patent) to stitch together its inherency analysis. A66.

This unsubstantiated analysis was an improper basis to invalidate the '096 patent as a matter of law especially given the conflicting testimony from Promega's experts as noted above. *See Alexsam, Inc. v. IDT Corp.*, 715 F.3d 1336, 1347-48 (Fed. Cir. 2013) (importance of expert testimony in technically complex cases).

In addition, a proper interpretation of the record reveals that the missing limitations of the claims of the '096 patent are ***not*** inherent in Smith '800. The district court interpreted the references in Smith '800 to "automation of the DNA sequencing process" as "Sanger" sequencing. It then posited that Sanger sequencing inherently included all the missing limitations of the '096 claims. However, to find those general references to "DNA sequencing" inherently disclose the Sanger method, the district court relied on a misinterpretation of the deposition testimony of inventor Smith. According to the district court, "Smith acknowledged at his deposition that these references to DNA sequencing [in Smith '800] describe the Sanger method." A66. But Smith only testified that the procedure referenced in Smith '800 patent was "*probably* done by a method *similar to*" Sanger sequencing. A19788 at 152:2-12.

The district court acknowledged in its obviousness discussion that there was no reason *a priori* to assume that Smith '800's fluorescent-labeled oligonucleotides

would necessarily work in Sanger sequencing. A70. As the district court observed: "[m]any prior art references—such as the Ruth '882 patent, the application for which was filed in February 1983—explained how to attach fluorescent tags to oligonucleotides, ***even though it was uncertain whether the resulting oligonucleotides could always be extended***." *Id.* (citing Ruth Rep. at 19-23).

Smith's testimony and the known uncertainty of whether the purportedly inherent disclosure could or would yield the invention of claims 62 and its dependents, or claim 66, is precisely the type of evidence that cannot properly support inherent anticipation—especially where Promega's experts are so definitive that one skilled in the art would not be enabled by such a disclosure to use the claims at issue. *See, e.g.*, *Cont'l Can*, 948 F.2d at 1269 ("The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient.) (emphasis in original). This is especially true on summary judgment where all reasonable inferences must be drawn in favor of the non-movant. *Anderson*, 477 U.S. at 255.

Finally, the district court ignored Life/Caltech's evidence that Smith '800 fails to enable the inventions of the '096 patent, which is required of an anticipating prior art reference. *Impax v. Aventis*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). Life/Caltech's technical expert Dovichi explained that "[w]hile . . . Smith

'800 patent mentions the possible use of these oligonucleotides in DNA sequencing, this offhand comment does not enable one with ordinary skill to hybridize the labeled oligonucleotide to a complementary sequence or to then extend the oligonucleotide by a polymerase." A11670 ¶ 150. Dovichi's opinions were not rebutted by Promega because its technical experts implicitly agree as noted above. This uncontested evidence that Smith '800 does not enable the claims of the '096 patent precludes a finding of anticipation.

Smith '800 does not and cannot anticipate the asserted claims of the '096 patent, either expressly or inherently. Accordingly, reversal of the district court's grant of summary judgment of anticipation is warranted and the defense should be rejected as a matter of law.

II. THE COURT ERRONEOUSLY GRANTED SUMMARY JUDGMENT OF OBVIOUSNESS-TYPE DOUBLE-PATENTING

As an alternative grounds for invalidating claims 62 (and its dependent claims) and 66 of the '096 patent, the district court concluded that they were subject to obviousness-type double-patenting in light of Smith '800. A73-76. This invalidity defense was never asserted by Promega. Apparently, Promega agreed with the Patent Office's conclusion, after reviewing Smith '800, that there was no obviousness-type double-patenting. A81 at References Cited (listing Smith '800 as

art considered and issued over). This issue was only raised in litigation by the district court *sua sponte* after the close of discovery.[12]

Apart from the procedural irregularities that gave rise to the district court's ruling, its substantive analysis was fatally flawed. It contradicted well-established precedent requiring comparison of only the ***claims*** of the two patents. *In re Kaplan*, 789 F.2d 1574, 1580 (Fed. Cir. 1986). Instead, the district court improperly expanded a limited exception to the rule set forth in *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1379 (Fed. Cir. 2012).

A. THE COURT IMPROPERLY LOOKED BEYOND THE CLAIMS OF SMITH '800 TO FIND DOUBLE-PATENTING

The district court's conclusion that the '096 patent and Smith '800 are not patentably distinct rested on a fundamental misapplication of double-patenting law.

The district court did not question the well-established rule that it is normally the *claims* that must be compared in the double-patenting analysis. *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992) ("[I]t is the claims that are compared when assessing double patenting."). Further, the district court did

[12] Promega failed to preserve this defense presumably because it concluded that it lacked merit. It was inappropriate for the district court to nevertheless pursue it on its own initiative. Additionally, by allowing only two days to prepare a response, the district court failed to provide reasonable time for Life/Caltech to formulate a response to this defense. *See, e.g.*, *Norse v. City of Santa Cruz*, 629 F.3d 966, 972 (9th Cir. 2010) (vacating summary judgment granted *sua sponte*, noting that "[t]wo days' notice did not comply with the requirements of Rule 56, and it did not afford [plaintiff] adequate time to prepare for the hearing, notwithstanding the proximity of the trial date").

not assert that the normal claim-to-claim analysis would lead to a finding of obviousness-type double-patenting. Rather, the district court's double-patenting analysis depended on going ***beyond*** the claims of Smith '800 by improperly expanding the *Lilly* exception.

As a threshold matter, any attempt to invalidate the '096 patent for double-patenting based on Smith '800 runs squarely at odds with the fundamental principles set forth in *Kaplan*. The district court cites *Kaplan* in cursory fashion, but never grapples with its outcome-determinative import.

In *Kaplan*, an inventor included in his solo application not only his own invention (a chemical compound), but also an improvement invention that he made jointly with a colleague. That joint invention is described in the application as a potential use for his solo invention. When Kaplan and his colleague sought a patent on their joint invention, the Patent Office issued an obviousness type double-patenting rejection because Kaplan's solo application disclosed the joint improvement invention.

This Court flatly rejected the double-patenting objection, explaining that the disclosure of Kaplan's joint invention was *not* part of the invention claimed in his solo patent:

> In effect, what the board did was to use a disclosure of appellants' own joint invention which had been incorporated in the Kaplan sole disclosure to show that

> their invention was but an obvious variation of Kaplan's claimed invention.

Kaplan, 789 F.2d at 1580.

The Patent Office contended that, because the disclosure of the joint invention could be said to support a claim, it was part of Kaplan's solo invention and thus invalid for double-patenting. This Court rejected that argument because the claims had support in other parts of the specification. *Id.* ("Moreover, that part of the Kaplan disclosure used to do this is a description of appellants' joint invention. The board's claim-support theory does not suffice to justify this anomalous result.").

Kaplan fits this case like a glove. Here, the district court combined the claimed chemistry invention in Smith '800 with the disclosure ***in the specification*** of DNA sequencing as a possible use of the claimed chemistry invention. But, just as in *Kaplan*, the use of the Smith '800 invention for DNA sequencing was specifically described as ***a separate invention of a different inventive entity***. It was not part of the Smith '800 invention itself.

Rather than distinguish *Kaplan*, the district court improperly expanded the "limited exception" set forth in *Lilly*. A74. *Lilly* provides a "limited exception to [the] customary framework" of double-patenting that allows for "limited consideration of teachings in an earlier-issued patent's specification" where "an earlier patent claims a compound, disclosing the utility of that compound in the

specification, and a later patent claims a method of using that compound for a particular use described in the specification of the earlier patent." *Eli Lilly*, 689 F.3d at 1379-80. In each of the cases discussed in *Lilly*, the reference patent described the "use" claimed in the second patent ***as part of the invention of the original patent***—none of them described that "use" as a different invention of a different inventive entity. *Id.*; *see also Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385-86 (Fed. Cir. 2003) (applying exception where plaintiff patented methods of using clavulanic acid to mitigate antibiotic resistance and pre-existing patent claimed clavulanic acid compositions and also disclosed their utility for antibiotic-resistance); *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (applying exception where asserted patent claimed methods of administering an anti-inflammatory drug and an earlier patent claimed the drug and disclosed the same method of administering it); *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1389 (Fed. Cir. 2010) (applying exception where asserted patent claimed an antiviral compound that proved useful for treating cancer and the claims of an initial patent covered the same antiviral compound and disclosed in the specification that the drug could be used for anticancer treatment).

In sum, this case is controlled by *Kaplan* because Smith '800 unquestionably discloses DNA sequencing as a separate invention created by a different inventorship entity. The *Lilly* exception only applies where the first issuing patent

discloses the "use" of the compound as an integral part of the invention claimed in that patent. That is not this case.

The district court's reliance on *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) is also misplaced. The district court cited *Otsuka* to support the proposition that it could consider the specification of Smith '800 and other evidence to determine whether an application of an earlier claim would have been obvious. A74. Although this Court deemed it appropriate in *Otsuka* to partially rely on findings under §103 in a double-patenting analysis, it also noted that the analysis should involve "whether one of ordinary skill in the art would have reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success." 678 F.3d at 1298. In *Otsuka*, the district court had considered other prior art, including a Nakagawa Declaration, to determine whether a person of ordinary skill would have reason to modify the earlier compound to make the compound of the later patent. *Id.* No similar analysis was performed by the district court here, nor could it have used *Otsuka* to find the claims of the '096 patent invalid. Indeed, as noted below, the undisputed record (by Life/Caltech's expert) demonstrates the claims of the '096 patent are patentably distinct from Smith '800. Further, the *Otsuka* court found the claims were *not invalid* because the claimed compounds were different and the prior art did not teach a person of ordinary skill in the art to pursue the necessary

chemical modifications. *Id.* at 1299-1300.

The district court erroneously applied the *Lilly* exception to use Smith '800 specification to determine obviousness-type double-patenting. This obviousness-type double-patenting decision should be reversed and no double-patenting found as a matter of law.

B. THE CLAIMS OF THE '096 PATENT ARE PATENTABLY DISTINCT FROM THE CLAIMS OF THE '800 PATENT

In addition, despite the prejudicially short period of time to respond to this defense (two days), Life/Caltech presented expert testimony that demonstrated that the claims of Smith '800 and the '096 patent are not only patentably distinct, but contain, at most, one limitation in common.

Life/Caltech's expert Batt explained that the claims of Smith '800 "do not include limitations that relate[] to or suggest adding: (i) a polymerase; (ii) a duplex comprising an oligonucleotide hybridized to a complimentary strand of DNA; (iii) covalently coupling an oligonucleotide to a fluorophore so as to allow chain extension by the polymerase; or (iv) compositions of four sets of oligonucleotides each with a distinguishable fluorescent label," all of which are required by the claims of the '096 patent. A17270 ¶ 11. Batt further opined that these four limitations were not merely obvious variations on the claims of Smith '800. A17271 ¶ 12. Finally, Batt explained that one could practice the claims of the '096 patent without practicing the claims of Smith '800. A17271 ¶ 14.

Promega submitted no evidence to the contrary even though it bore the burden of proving this defense by clear and convincing evidence. *Symbol Techs.*, 935 F.2d at 1580. Of course, as explained above, Promega's technical experts are convinced that even the fulsome Smith 1986 article is insufficient to place the invention in the public's hands so the claims of the '800 patent surely cannot do so. There is no obviousness-type double-patenting here as a matter of law.

III. THE DISTRICT COURT HAD NO BASIS TO FIND CLAIM 67 OF THE '096 PATENT OBVIOUS

The district court invalidated claim 67 of the '096 patent as obvious based on a combination of art of its own making: Ruth '882 and Tsuchiya. A70-73. In its flawed analysis, the court misconstrued the art through hindsight and selective quotation, ignored this Court's precedent, and refused to acknowledge the undisputed objective indicia of non-obviousness. These failings require reversal. There is, at a minimum, a material factual dispute as to the obviousness of claim 67.

A. THE DISTRICT COURT'S PREMISE REGARDING THE SCOPE AND CONTENT OF THE ART WAS FLAWED

The core of the district court's obviousness analysis—that it would have been "straightforward to tag four different sets of oligonucleotides with four distinguishable fluorophores" is unsupported and insufficient. A70. But the district court never answers the question it begs: If it was so straightforward and

obvious to create four sets of oligonucleotides, each with distinguishable fluorescent tags, how come none of the many workers in the field, including Promega's experts, were able to do so? Indeed, no prior art to Claim 67, including Ruth '882, suggests oligonucleotides labeled with fluorescent tags having multiple different, distinguishable colors. As explained above, Ruth himself insists that Dr. Smith's landmark 1986 article does not even enable this claim and Dr. Van Ness documents his belief of how hard it would be to arrive at working fluorescent labels in the invention. The testimony of Promega's experts should be the end of this obviousness defense standing alone. Because the district court's premise regarding the content of the art was so wrong, its obviousness finding as a matter of law necessarily fails.

The district court cited the Ruth '882 patent, at column 3, line 56 to column 4, line 3 for the proposition that labeling of oligonucleotides "could be done using fluorophores with many different spectra—colors distinct enough from each other to be distinguishable by a computer." A70. However, the cited text from Ruth '882 actually describes the potential use of different ***types*** of labels, such as "colorimetric, fluorescent, luminescent, or antibody- or other ligand-mediated detection" or "a radioactive moiety," rather than different colors of fluorescent labels. A148 at 3:67-4:2.

Because of the beliefs of its experts to the contrary, Promega offered no expert testimony that Ruth '882 or any other art disclosed oligonucleotides labeled with fluorescent tags having multiple different, distinguishable colors as required by claim 67. Instead, the district court relied on its own lay misinterpretation of Ruth '882. The district court's substitution of its own opinions and fact-finding for expert testimony was error.

Even if the district court had been correct (and it is not) that it would have been "straightforward to tag four different sets of oligonucleotides with four distinguishable fluorophores," this does not support its obviousness ruling. Such an assumption only suggests that it might have been possible to generate oligonucleotides labeled with fluorescent tags having multiple different, distinguishable colors—and yet no one did (until the '096 inventors). In fact, as Life/Caltech's expert pointed out, Ruth '882 expressed concern that modification of oligonucleotides might disrupt hybridization as well as interfere with the workings of the enzymes needed to extend an oligonucleotide along a complementary strand. A11662-3 ¶ 129 (citing A147 at 2:5-8). *See also* A148-49 at 4:66-5:16.

Moreover, a mere possibility is legally insufficient—there must be "a finite number of identified, predictable solutions" that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007). Even if the art cited by the

district court provided the ***possibility*** of multiple labels (and it did not), obviousness cannot stand on that ground.[13] In light of that state of the art (and Ruth '882's express doubt that the modified oligonucleotides would work), a person of ordinary skill would not have had a reasonable expectation of success in creating the composition of claim 67 even if motivated to do so.

B. THE DISTRICT COURT ERRED IN FINDING A REASON TO COMBINE AND MODIFY THE ART

The district court also had no basis to determine that a person of ordinary skill would have been motivated to combine multiple sets of oligonucleotides labeled with different types of distinguishable fluorophores. A70-72.

The district court first erred by stating that the "reason biochemists would mix four distinguishable sets of fluorophores in Sanger sequencing is to avoid having to run four separate reactions to measure the tagged DNA strands." A71. This statement was supported by no expert testimony or record evidence and essentially assumes the invention. In fact, Promega never made this argument—nor could it given the views of its experts.

The district court's obviousness determination was infected with hindsight bias, using the specification of the '096 patent as a guide. This Court has

[13] The district court also omitted a key limitation of claim 67: that the fluorophores not only be distinguishable, but be of "different types." The art the district court relied upon did not encompass multiple types of fluorophores. A70 (citing A148 at 3:56-4:3).

repeatedly cautioned that "[c]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in the suit." *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (internal quotations omitted).

The specification of the '096 patent describes Sanger sequencing (*e.g.*, 1:65-2:23; 5:51-57), how electrophoresis was used to analyze the products of the sequencing reaction (*e.g.*, 2:13-19; 5:54-56), how the prior methods required four separate reactions and four separate electrophoretic gel tracks for analysis (*e.g.*, 2:16-23; 5:54-56), how the invention improved upon the state of the art "by the use of a set of four chromophores or fluorophores with different absorption or fluorescent maxima," (5:57-60) and how they are run in single electrophoretic columns or lanes where the different fluorescent colors distinguish the oligonucleotides (*e.g.*, 4:50-67; 8:27-44; Fig. 3). Indeed, the figure set forth at page 12 of the court's ruling is virtually identical to the content of Figure 3 of the '096 patent, as both depict the prior multiple lane electrophoretic separation and the inventive single lane, four-color separation.

The district court unhelpfully quoted from Tsuchiya to try to find a motivation to combine or modify. Specifically, the district court asserted that "[a] person of ordinary skill who read the abstract would have been motivated to use its

multicolor technique when analyzing DNA probes, in order to increase the number of probes he could process on a single gel." A72. This was purportedly based on the following statement in Tsuchiya:

> [A] lot of information can be obtained form [sic] one column by using multi-color labeling. Now we are developing an automated real time fluorescence detection gel electrophoresis system.

A72. However, elsewhere Tsuchiya makes clear that the "multi-color process" did not yet exist, and was only at best a hoped for plan for future development. A17188 ("***If multicolor labeling is possible,*** a great deal of information can be collected via a single analysis channel."). At best, this is an invitation to experiment, and provides no "reasonable expectation of success in doing so," as required by the patent law. *See, e.g.*, *Procter & Gamble v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). And given Ruth '882's expressed fear of the adverse consequences of oligonucleotide modifications, there would have been no motivation, let alone expectation of success, in doing so.

To support its decision, the district court also truncated the second sentence in Tsuchiya to suggest that the authors had developed, or were developing, a four-color electrophoresis system. The unedited language, when read in context, reveals that Tsuchiya discusses the use of only one fluorophore—ethenoadenosine—and not four different and distinguishable fluorophores, as claim

67 requires. *See* A17188 ("Fluorescent labeling of DNA via ethenoadenosine (eA) is accomplished in the following manner . . . ."). The full text is reproduced below, with the omitted language emphasized:

> A lot of information can be obtained form [sic] one column by using multi-color labeling. Now we are developing an automated real time fluorescence detection gel electrophoresis system ***using etenoadenosine [sic] as a fluorophore which can label DNA without changing DNA structure much and has a high fluorescence quantum yield.***

A17192. The district court's selective quotation from Tsuchiya obviously was its attempt to fill in the missing elements from the '096 patent through the improper application of hindsight, and thus constitutes reversible error.

C. THE DISTRICT COURT ERRED IN NOT PROPERLY CONSIDERING OBJECTIVE INDICIA OF NON-OBVIOUSNESS

Finally, the district court erred by refusing to consider Life/Caltech's evidence regarding the objective indicia of non-obviousness. As this Court has commanded, "a district court must ***always*** consider any objective evidence of nonobviousness presented in a case." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010) (emphasis in original).

Here, there existed objective evidence of non-obviousness that was unrebutted by Promega. For example, the now-ubiquitous use of the invention is strong evidence that it fulfilled a long-felt need; indeed, the district court itself

characterized the '096 patent as a "major" invention. A40. Likewise, it was undisputed that Promega's products practicing the invention have achieved significant commercial success, and that Promega and others have sought to license the inventions contained in the '096 patent.[14]

The district court ignored all of this evidence in its rush to invalidate the patent. The failure of the court to address the secondary indicia of non-obviousness requires reversal.

IV. THE DISTRICT COURT ERRED BY INVALIDATING METHOD CLAIM 62 AND DEPENDENTS FOR LACK OF WRITTEN DESCRIPTION

The district court further erred by invalidating claim 62 and its dependents for lack of written description. A76-77. The district court invalidated these claims because they encompass the use of the invention for techniques that "hadn't been invented in 1984 when the application for the '096 patent was first filed." A77.

In effect, the district court's analysis improperly required the '096 specification to disclose future DNA analysis applications of the ground-breaking inventions of these claims.

A. THE DISTRICT COURT MISAPPLIED THE LAW OF WRITTEN DESCRIPTION

The district court's conclusion that the claims do not meet the requirements

[14] There are also other secondary indicia, such as praise by others. For example, Life/Caltech's expert Dovichi, highlighted the large number of academic citations to papers authored by the inventors that explained the invention. A11676-77. The district court improperly excluded this expert opinion. A48-49.

of §112 is flat wrong. Whether a claim is supported by an adequate written description is a factual inquiry in which the fact-finder must determine whether the specification will "allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). Courts look to whether the disclosure of the application relied upon "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.*

Here, the district court based its written description conclusion on several incorrect premises.

1. THE SPECIFICATION NEED NOT DESCRIBE MORE THAN ONE EXAMPLE

First, the district court incorrectly found the exemplification of the claimed method in the '096 patent in one context, DNA sequencing, was insufficient to support claims that cover the use of the method for other DNA analysis applications. The district court explained that the claim "reaches any method of obtaining information about a genetic sequence." A76-77. The district court then held that "claim 62 of the '096 patent claims all methods of nucleic acid sequence analysis, but the patent specification describes only one such method (the Sanger method)" and that because "Promega's multiplex STR analysis is not a new use of the Sanger method . . . Claim 62 and its dependent claims are therefore invalid."

A77.

The district court's conclusion violated the principle that "[a] patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009); *see also Bilstad v. Wakalopulos*, 386 F.3d 1116, 1123 (Fed. Cir. 2004) ("'We cannot agree . . . that in every case where the description of the invention in the specification is narrower than that in the claim there has been a failure to fulfill the description requirement in section 112.'") (quoting *In re Smythe*, 480 F.2d 1376, 1382 (C.C.P.A. 1973)).

For example, in *In re Rasmussen*, 650 F.2d 1212 (C.C.P.A. 1981), the claim was to a method of manufacturing a thermal insulating member, and the adequacy of the written description was challenged on the grounds that the claims recited "adheringly applying" one layer to another while the specification only described a single manner of "adheringly applying" the layers. In finding adequate written description, the district court explained that the fact "that a claim may be broader than the specific embodiment disclosed in a specification is in itself of no moment." *Id.* at 1215.

Here, Promega conceded that, under the district court's claim construction, Promega's accused STR analysis methods infringe. That the specification of the '096 patent exemplifies those same steps in a different context (*i.e.*, sequencing) is

not relevant to the adequacy of written description. The issue is solely whether the steps actually recited in claim 62 and its dependent claims are adequately described in the '096 specification. Promega has conceded that they are. *See* A10848-50.

2. SECTION 112 DOES NOT REQUIRE THE SPECIFICATION TO DESCRIBE ALL FUTURE EMBODIMENTS

It was also error for the district court to invalidate claim 62 and its dependents on the grounds that Promega's conceded mode of infringement is not specifically described in the specification. Federal Circuit case law clearly "allows for after-arising technology to be captured within the literal scope of valid claims that are drafted broadly enough[.]" *See Innogenetics, N.V. v. Abbot Labs.*, 512 F.3d 1363, 1371–72 (Fed. Cir. 2008); *see also SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 878–80 (Fed. Cir. 2004) (finding that the claim limitation "regularly received television signal" was broad enough to encompass digital signals even though televisions that could receive digital signals did not exist as of the filing date).

The district court found that, because Promega performed the steps of claim 62 via PCR reactions, which was not yet invented in 1984, there could be no written description in the '096 patent to support a claim that would cover its infringement. A77. Written description analysis, however, is not made with regard to an infringing product, but focuses solely on whether the specification demonstrates that the inventor was in possession of the invention. As this Court

has recognized, demonstrating possession of the invention does not require that an inventor describe any and all possible or future applications of the invention. *Ariad Pharms.*, 598 F.3d at 1351.

Simply because the later-developed products infringe the claimed method does not mean that the inventors were required to describe those methods, which were not known to a person of ordinary skill, with particularity in the patent specification in 1984. By invalidating the '096 patent for not describing the use of the claimed fluorescent molecules in conjunction with the subsequently-developed PCR technique, the district court ignored this Court's precedent, and its ruling should be reversed.

3. THE DISTRICT COURT ERRED IN TREATING CLAIM 62 AS A GENUS CLAIM

Finally, the district court wrongly analyzed claim 62 under the rubric of "genus" and "species," an analysis that is not statutory but refers to a patent practice that arose from inventions of chemical compounds such as pharmaceuticals, where an inventor attempted to claim not only the specific chemicals that had been invented, but all others that had similar properties. *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1341 ("The claims are thus genus claims, encompassing the use of all substances that achieve the desired result of reducing the binding of NF-β to NF-β recognition sites").

In the life sciences context, practitioners and courts applied the concept

when scientists began sequencing genes and sought to claim those genes as patentable inventions. A body of law arose around the distinction of claiming a particular DNA gene sequence versus a more generic claim for all possible DNA sequences that would perform the function of the gene. *See, e.g.*, *Billups-Rothenberg, Inc. v ARUP, Inc.*, 642 F.3d 1031, 1036-38 (Fed. Cir. 2011) (claim failed written description requirement for generically claiming all possible DNA mutations to a particular gene without revealing the sequence for any specific mutations).

Recognizing the potential for abuse, this Court held that an adequate written description of a claimed genus required a description of the "structural" features of a claimed genus, not merely its function. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

The genus/species claim distinction is inapplicable to claim 62. Claim 62 makes no attempt to claim a whole category of compounds through the use of functional language, as genus claims do. Instead, claim 62 involves the use of fluorophore-labeled oligonucleotides that can be extended by a polymerase. It merely claims the subject matter in an "open" format so as to encompass those steps regardless of whether they are performed in the context of the practice of additional, unclaimed method steps or in other contexts involving unclaimed elements.

The district court failed to appreciate that the inventors of the '096 patent were entitled to claim the use of the method in all contexts in which those method steps may be performed regardless of whether all ways of implementing the method are expressly described in the specification. And even if this could be considered a genus claim—which it is not—the scope of the claim is supported because it is undisputed that the inventors described in detail at least one of the species, a working method of genetic analysis.

V. THE EXCLUSION OF LIFE/CALTECH'S DAMAGES EXPERT WAS CONTRARY TO WELL-SETTLED DAMAGES LAW

The court abused its discretion by excluding the reasonable royalty testimony of Life/Caltech's damages expert Greene. A49-51.

For damages, Life/Caltech sought a reasonable royalty. For sales within the field of use in the parties' cross-license, Life/Caltech sought contract damages, i.e., the prior agreed rate of 2%. *See* A11918 ¶ 357. However, for sales outside the field of use—sales to which Life/Caltech would have exclusive rights per the agreement of the parties—Greene calculated a reasonable royalty of 10% based upon a hypothetical negotiation pursuant to the *Georgia-Pacific* factors (A11858-918 ¶¶ 123-357), a framework repeatedly accepted by this Court. *See i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 853-54 (Fed. Cir. 2010) (affirming a damages expert's analysis of a "hypothetical negotiation" between the parties and the *Georgia-Pacific* factors to determine a reasonable royalty rate). To reach 10%,

Greene began with the contract rate of 2% and analyzed the relevant patent license agreements from both Life (showing what Life would out-license for its technology) and Promega (showing what Promega would pay to in-license technology for the products at issue), as well as prior trial testimony of Promega witnesses about licensing at 12% relating to DNA sequence analysis reagents and related products, including agreements with rates up to 15%. A11859-901 ¶¶ 128-307; A11911-914 ¶¶ 343-349. The court rejected this analysis in its entirety.

At the heart of the district court's analysis is its factual finding that Greene's "report does not identify the six licenses he relied on or explain why they were the most relevant, and he could not identify them at the *Daubert* hearing." A50. This is not true. Greene's report persuasively discusses these six licenses and others at length. A11860-81 [USB (¶¶ 129-140; Amersham (¶¶ 141-153), Shimadzu (¶¶160-173), Visible Genetics (¶¶ 174-191), Kit Manufacturing Licenses (¶¶ 194-206) and Probe Manufacture Agreements (analyzed as a set) (¶¶ 207-221). This is a fundamental factual error by the district court that distorts its whole analysis, warranting reversal. Greene's inability to list these licenses without referencing his report when cross-examined by the district court is no reason to conclude that such licenses have not been identified in the record – and certainly should not form the foundation for striking his entire opinion.

In addition, contrary to the district court's criticism, Greene did consider the

2006 Cross License and identified key differences between the actual negotiation in 2006 and the hypothetical negotiation that would have occurred in 2012. Eight pages of Greene's expert report reflect this analysis. *See* A11852-54 ¶¶ 100-103; A11855-58 ¶¶ 109-122; A11859 ¶ 128. To the extent the court took issue with Greene's failure to "attempt to quantify the impact of these differences," the court relied on its own fact-finding about the weight of the testimony, rather than its reliability.

The court compounded its error by requiring that Greene should have "estimat[ed] . . . the profits that Promega would have lost had it not obtained a license . . . or the share of those otherwise-lost profits that Life Tech could have extracted in negotiating a license." A51. However, this type of quantification is not required for reliable testimony. It may the subject of cross-examination, but there is no precedent that requires such hypothetical analysis as a threshold condition for presenting a reasonable royalty case to a jury.

The court also criticized Greene for not considering "the totality of the circumstances" and purportedly failing to properly "quantify the impact" of each factor he considered. A50. *Georgia-Pacific*, however, specifically acknowledges that "there is no formula by which the[] factors can be rated precisely in the order of their relative importance or by which their economic significance can be automatically transduced into their pecuniary equivalent." *Georgia-Pacific Corp.*

v. U.S. Plywood Corp., 318 F. Supp. 1116, 1120-21 (2d Cir. 1971). A reasonable royalty damages analysis "necessarily involves an element of approximation and uncertainty" and therefore a precise computation is not required. *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1325 (Fed. Cir. 2009). By requiring a precise computation, the court imposed an improper and impossible standard for reliability.

Criticisms regarding Greene's ultimate conclusions regarding the degree of comparability between actual licenses and the hypothetical license also were not a proper basis to exclude. *See i4i*, 598 F.3d at 852; *see also ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1333 (Fed. Cir. 2012) ("The degree of comparability of the . . . license agreements as well as any failure on the part of [an] expert to control for certain variables are factual issues best addressed by cross examination and not by exclusion.").

Where, as here, the methodology was "sound, and the evidence relied upon sufficiently related to the case at hand, disputes about the degree of relevance or accuracy (above this minimum threshold) may go to the testimony's weight, but not its admissibility." *i4i* , 598 F.3d at 852. The court's ruling regarding Greene should therefore be reversed, and Greene should be permitted to testify regarding a reasonable royalty rate at trial.

CONCLUSION

The Court should reverse the district court's judgment below in accordance with the relief requested above.

Dated: September 9, 2013 Respectfully submitted,

By /s/ Edward R. Reines

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ADDENDUM

Table of Contents

TAB 1

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS

PROMEGA CORPORATION,	)	
Plaintiff,	)	No. 13 C 2333
	)	
v.	)	Judge Richard A. Posner
	)	
APPLIED BIOSYSTEMS, LLC,	)	
LIFE TECHOLOGIES CORPORATION,	)	
and CALIFORNIA INSTITUTE OF	)	
TECHNOLOGY,	)	
Defendants.	)	

ORDER OF APRIL 4, 2013

On March 28, 2012, I conducted a hearing on claims construction for U.S. Reissued Patent No. RE43,096, and Promega and the defendants' (whom I'll refer to collectively as Life Tech) motions for summary judgment on infringement, reissue recapture, patent prosecution laches, and breach of a 2006 cross-licensing agreement between the parties. On the basis of that hearing and the parties' briefs, I adopt the following claim constructions, see *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995) (en banc), affirmed, 517 U.S. 370 (1996), and resolve each summary judgment motion.

Claim Construction

"A method of nucleic acid sequencing analysis." The first claim construction dispute concerns the preamble to claim 62 of the patent, which describes "a method of nucleic acid sequencing analysis." The parties dispute whether this language is meant to limit the scope of the invention in the body of the claim, which defines the method's steps. They also dispute the meaning of the phrase.

"In general, the purpose of a claim preamble is to give context for what is being described in the body of the claim," rather than to limit the scope of the claimed invention, *Symantec Corp. v. Computer Associates Int'l, Inc.*, 522 F.3d 1279, 1288 (Fed. Cir. 2008). But the preamble may be limiting "if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *Id*. And that is the case here. Without the preamble, claim 62 merely describes a method of extending a DNA strand that has been fluorescently tagged. The process is meaningful only because it allows a

biochemist to obtain information about the DNA strand—indeed, that is what the inventors said distinguishes the invention from prior art that succeeded in fluorescently tagging a DNA strand, but that could not be used in DNA sequencing operations. I therefore construe the preamble to claim 62 as limiting.

Although the preamble is limiting, nothing in the patent limits its meaning, as Promega suggests, to "determining the identity and order of nucleotides in a DNA molecule at a single nucleotide resolution"—that is, determining each and every nucleotide in the strand (for example, ATTCGTACGAT). If the inventors wanted to so limit their claim, they could have claimed a "method of DNA sequencing," as they did repeatedly in earlier patent applications, and indeed in the preamble to claim 64 of the current patent. Instead, in drafting claim 62, they chose the broader term "nucleic acid sequence analysis," which encompasses any type of analysis of a genetic sequence, even if not at a single nucleotide resolution. Such analysis might reveal, for example, the number of times the strand repeats a particular pattern of nucleotides (e.g. GATAGATAGATA) or the existence of a mutation in the sequence. Life Tech lists several other examples: "fragment analysis, short tandem repeat analysis, restriction fragment length polymorphism, Southern hybridization, chain termination sequencing, and microsatellite loci analysis." At least as early as 1992, the inventors made it clear to the patent examiner that the "claimed invention is not limited to the use of fluorescent compounds to actually sequence nucleic acids," as the examiner stated in a July 2, 1992 action on the patent application.

Therefore, I construe the preamble "a method of nucleic acid sequence analysis" to limit Life Tech's claims to "any method of obtaining information about a genetic sequence."

"Oligonucleotide." Life Tech suggests that the remaining disputed terms should be given their "plain and ordinary meanings," but that phrase is a misnomer in this context. How can a technical term such as "oligonucleotide" have a plain meaning to a layperson? What Life Tech really means is that each term has a widely accepted meaning among biochemists, which is used in the patents. Promega responds that the patent adopts a narrower, idiosyncratic meaning for each term, limited to sequencing reactions. It correctly points out that the inventor is free to act as his own lexicographer by providing a definition in the specification that is narrower than a term's usual usage. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–14 (Fed. Cir. 2005) (en banc). But in each case Promega's evidence that the inventors have done this is very weak.

Life Tech proposes that "oligonucleotide" be construed as "a short polymer, in general a chain of under 200 bases, consisting of a linear sequence of four nucleotides in a defined order." This construction is based on a description of "oligonucleotide" added to the specification of the '096 patent on reissue, see col. 3, ll. 6–7, and Life Tech cites in further support two patent applications cited in the '096, which explain that strands

under 200 bases are generally termed "oligonucleotides," while longer chains are called "polynucleotides." U.S. Patent No. 4,948,882, col. 2, ll. 32–34; U.S. Patent No. 5,541,313, col. 2, ll. 32–34.

Promega does not contest that the defendants' definition is accepted among biochemists. Instead it argues that the patent uses its own definition of "oligonucleotide." It first points to the specification's statement that "primers" must have four narrow characteristics: "1) They must have a free 3' hydroxyl group to allow chain extension by the polymerase. 2) They must be complementary to a unique region 3' of the cloned insert. 3) They must be sufficiently long to hybridize (that is, attach to an existing single strand of DNA) to form a unique, stable duplex. 4) The chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase." (col. 5, l. 66–col. 6, l. 6.) The mention of a "cloned insert" (a DNA strand with a known sequence attached to an unknown strand to facilitate replication) suggests that the primers are useful only in sequencing reactions (which involve replicating an unknown strand). In the 2001 litigation over the '748 patent, as I'll explain in more detail later on, the district court adopted this construction and thereby limited the term "primer" to the subset of primers used in DNA sequencing applications. *Promega Corp. v. Applera Corp.*, 2002 WL 32355680 at *10–13 (W.D. Wis. 2002).

Promega argues that the specification requires "oligonucleotide" to have the same construction as "primer." It notes the patent's statement that "the primer is either a synthetic oligonucleotide or a restriction fragment" (col. 2, ll. 5–6), but this does not logically imply that all oligonucleotides are primers, as Promega suggests. (All cats are either female or male, but not all females are cats.) The specification also uses the word "oligonucleotide" (or "oligonucleotide primers") to refer to the primers in sequencing reactions; but this again does not mean that the word always refers to primers. As a counterexample, the specification's Example IV describes the process of attaching the fluorescent tags to DNA strands which may or may not be sequencing primers. (Col. 9, l. 28–col. 10, l. 50.) The example consistently uses the term "oligonucleotide" instead of "primer," further indicating that the two are not interchangeable.

Promega also claims that a narrow definition of "oligonucleotide" is required because of statements the inventors made during prosecution of the '748 to distinguish various pieces of prior art. The inventors said that the claimed oligonucleotides are shorter than the "polynucleotides" claimed in one reference (Draper); to distinguish other references, they added that the oligonucleotides claimed in the patents are extendable and capable of hybridizing to a specific sequence. These statements are either consistent with the usual meaning of "oligonucleotide" or relate to other terms in the asserted claims. Promega has not shown that the inventors departed from the term's usual meaning, and I therefore adopt Life Tech's proposed construction.

"Four sets of oligonucleotides." Promega suggests that this term be defined as "four sets of oligonucleotides capable of generating size-nested sets of DNA fragments that contain, in their collection of lengths, the information necessary to define a sequence of oligonucleotides." The phrase "four sets" is a common English phrase that is not used counterintuitively in the '096 patent. Having already construed "oligonucleotide," I agree with the defendants that this term does not require construction.

"Complementary strand of DNA." In biochemistry, the word "complementary" refers to base-pairing rules. In a double strand of DNA, each nucleic acid base in one strand pairs with only one base in the other strand—adenine (A) with thymine (T), and cytosine (C) with guanine (G). Life Tech therefore proposes that the term be construed as "a strand of DNA with corresponding molecules."

Promega does not dispute that this is the accepted meaning of the phrase, but it argues that the phrase as used in the '096 patent means "a cloning vector"—which, as I said earlier, is a known DNA sequence attached to an unknown sequence to facilitate replication. It's true that the specification sometimes uses the phrase "complementary strand of DNA" to refer to a cloning vector, but only when it is already clear that the strand is a cloning vector. This does not establish that the phrase always refers to cloning vectors. And the patent also describes a "complementary stretch of DNA" used in fluorescent labeling (that is, prior to sequencing), and this strand is not a cloning vector (col. 6, ll. 65–66). I adopt Life Tech's proposed construction.

"Duplex." The defendants' proposed construction is "a double-stranded part of a nucleic acid molecule," a generally accepted biochemical definition. Promega responds only that the definition of duplex is "inextricably linked" to its other proposed constructions limiting the claim terms to sequencing reactions, which I have already rejected. I adopt Life Tech's proposed construction.

"Polymerase." Life Tech proposes to construe the term as "an enzyme capable of catalyzing the formation of a polymer from monomers." (A "polymer" is a molecule which consists of linked repeating units; these units are smaller molecules called "monomers.") Promega's proposed construction is "polymerase used to perform sequencing reactions, such as the Klenow fragment of DNA polymerase."

Once again Promega attempts to artificially limit a term's construction to DNA sequencing reactions—in this case by adding words to the construed term itself. While Promega is correct that the specification mentions polymerase only in the context of sequencing, that alone does not indicate that the inventors limited the term's meaning to sequencing and thereby deviated from the accepted scientific meaning. Life Tech's construction is adopted.

"Fluorophore." Life Tech construes the term to mean "a fluorescent molecule or molecular component." Promega does not contest that this is the accepted biochemical definition, but it proposes the definition "fluorescent tag that may be coupled to an oligonucleotide to establish a correlation with a distinct nucleotide and to allow for the identification of said molecule." Promega's construction describes the function of the fluorophore in the sequencing process, but nothing in the specification limits the term itself to that process. Fluorophores are useful in reactions other than sequencing, and neither the specification nor the prosecution history indicates that the inventor meant that term to narrow the term "fluorophore" to a tag used in sequencing, which is the import of Promega's proposal. I adopt the defendants' proposed construction.

"specifically hybridized to the complementary strand of DNA." Although neither party has formally requested a construction of the phrase "specifically hybridized" or proposed a concrete definition, Promega's opposition to Life Tech's infringement allegations requires a very specific construction of the term. The asserted '096 claims describe an oligonucleotide "specifically hybridized" to a complementary DNA strand—that is, engineered to bind to a locus having a complementary nucleotide sequence. Promega contends that the oligonucleotides it provides as part of its DNA fingerprinting systems aren't "specifically hybridized" to their intended locus because they can potentially bind to more than one locus of the genomic DNA being tested. This argument is premised on a construction of "specifically hybridized" that covers only hybridization to a unique locus, and is therefore a belated request for additional "rolling" claim construction, e.g. *Pfizer, Inc. v. Teva Pharmaceuticals, USA, Inc.*, 429 F.3d 1364, 1377 (Fed. Cir. 2005). I must construe the claim term before evaluating infringement. Cf. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008).

Promega's proposed interpretation is unreasonably narrow. The asserted '096 claims describe oligonucleotides that are useful because they bind to a specific locus; the claims say nothing about whether that locus must be unique. For certain nucleic acid sequence analysis applications—DNA fingerprinting, for example—it's clear that the locus needn't be unique because chains extended from erroneously-bound oligonucleotides are easily disregarded. Other applications like DNA sequencing do rely on the oligonucleotide's binding to a unique locus, but the patent isn't limited to DNA sequencing, as I explained above. Promega hasn't explained why the '096 inventor would have sought to cover only this latter subclass of applications, thus excluding applications involving oligonucleotides hybridized to non-unique loci from the scope of its patent. More likely the inventor intended oligonucleotides "specifically hybridized to the complementary strand of DNA" to refer to the entire class of oligonucleotides targeted at a specific DNA locus. I construe the phrase to mean "hybridized to a specific locus on a complementary strand of DNA, even if that locus is not unique."

Infringement

Life Tech has moved for summary judgment of infringement as to Promega's products in the field of DNA fingerprinting, a method of analyzing two DNA samples to determine whether they came from the same person. Promega's products work by comparing the length of short tandem repeat sections of each sample. A short tandem repeat (or STR) locus is a DNA region where the same nucleotide sequence is repeated multiple times (e.g. CTACTACTACTA), with the number of repetitions varying from person to person. If two samples' corresponding STR regions are the same length, it means they repeat the same number of times, and it's more likely that they came from the same person. But any given STR locus isn't so variable that a single match is conclusive, so multiple STR loci must be measured and compared. Each match increases the confidence of a valid identification.

For the purpose of these motions, Life Tech asserts that Promega's PowerPlex 16 HS System is representative of its DNA fingerprinting products. See "PowerPlex 16 HS System," www.promega.com/products/genetic-identity/str-analysis-for-forensic-and-paternity-testing/powerplex-16-hs-system/ (visited March 31, 2013). I will consider that product when evaluating Life Tech's motions for summary judgment of infringement. Promega formally disputes that it stipulated that the PowerPlex 16 HS System is representative of Promega's STR-analysis products, but it has provided no explanation of how its other products may differ. If the following opinions about Promega's infringement of the '096 patent do not apply to Promega products other than the PowerPlex 16 HS System, Promega may move to limit the scope of this order. Any such motion must clearly address how the additional products differ from the PowerPlex 16 HS System, and why such differences are relevant to infringement of the asserted claim terms.

The PowerPlex 16 HS System performs DNA fingerprinting by comparing sixteen different STR loci between the two samples. In order to measure the length of each STR locus, it must be "amplified" by creating multiple copies. Amplification involves fluorescently-tagged oligonucleotides that are complementary to the nucleotide sequence immediately preceding each STR region. The tagged oligonucleotide binds to the target locus of the sample and is extended using a polymerase to complete a complementary copy of the STR region. The PowerPlex technical manual contains instructions for amplifying and measuring the STR copies, and Promega provides the necessary polymerases and tagged oligonucleotides to perform the process.

Life Tech is entitled to summary judgment of infringement if it presents undisputed evidence that each claim limitation is present in Promega's product, such that no reasonable jury could find otherwise. *Innovention Toys, LLC v. MGA*

Entertainment, Inc., 637 F.3d 1314, 1319 (Fed. Cir. 2011). Life Tech alleges that Promega's products infringe claim 62 of the '096 patent and two of its dependent claims. Claim 62 reads:

> 62. A method of nucleic acid sequence analysis, comprising extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product, wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA, and wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

The preamble, "a method of nucleic acid sequence analysis," is a claim limitation, and it means "a method of obtaining information about a genetic sequence." Promega's product measures and compares the length of specific STR sections. Promega doesn't dispute that the length of an STR strand is information about a genetic sequence, so I determine that its products practice the limitation articulated by the preamble.

The claim is next limited to the process of "extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product." As I explained above, this is exactly what takes place when a DNA sample is amplified as part of the PowerPlex 16 HS System. Each tagged oligonucleotide supplied by Promega binds to a complementary section of the sample strand to form a duplex and is then extended by a polymerase. The product is "labeled" by the fluorescent tag attached to the oligonucleotide. The excerpts from the PowerPlex 16 HS System Technical Manual provided by Life Tech confirm this description. Promega's expert opinions to the contrary are based on Promega's rejected claim constructions, and therefore don't create a triable factual dispute.

Claim 62 is further limited to processes "wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA." Promega concedes that it provides nucleotides engineered to hybridize to specific locations in a DNA sample, but disputes that these oligonucleotides are *specifically* hybridized because each can potentially bind to multiple loci on human genomic DNA. Having rejected the claim construction on which this argument is premised, I conclude that the PowerPlex 16 HS System practices this limitation.

Finally the claim requires that "the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase." Promega agrees that Figure 23 of the PowerPlex 16 HS System Technical Manual "evinces fluorescently labeled amplification products." It is undisputed (given my claim constructions) that the amplification products contain oligonucleotides labeled by being coupled to a fluorophore by means of a linker molecule. Promega counters by citing its expert's rebuttal report but to no avail; the expert's discussion is specific to the term "fluorescent nucleotides," which appears only in claim 70 (discussed *infra*). If anything, the expert's

discussion of linker molecules confirms that the fluorophore is covalently bonded to the oligonucleotide.

Life Tech has produced evidence indicating that the PowerPlex 16 HS System practices every limitation in '096 claim 62. The only factual disputes Promega raises in opposition rely on its proposed claim constructions, which I have uniformly rejected. Therefore I GRANT partial summary judgment that Promega's PowerPlex 16 HS System literally infringes claim 62, without taking any position on the validity of the claim. *Pandrol USA, LP v. Airboss Ry. Products, Inc.*, 320 F.3d 1354, 1365 (Fed. Cir. 2003).

Life Tech also alleges that the Promega's products infringe claim 63, which is dependent on claim 62. It reads:

> 63. The method of claim 62, further comprising separating said labeled extension product from said duplex

Life Tech, citing the PowerPlex 16 HS System Technical Manual explains that a step in the application protocol requires denaturing the amplified STR duplexes—heating the mixture until the nucleotide bonds between the tagged strands (the "labeled extension product") separate from the sample DNA. This constitutes "separating said labeled extension," as described in claim 63. Promega disputes the construction of "duplex," but doesn't quibble with Life Tech's characterization of the denaturation process. Partial summary judgment of literal infringement of claim 63 is therefore GRANTED, without taking any position on the validity of the claim. *Id*.

Life Tech also alleges that Promega's products infringe claim 70, which is also dependent on claim 62. It reads:

> 70. The method of claim 62, wherein substantially all molecules of the labeled extension product individually comprise a single fluorescent nucleotide.

As I stated earlier, Promega tags each oligonucleotide by attaching a fluorophore to a constituent nucleotide by means of a linker molecule. Promega argues that this doesn't count as a "fluorescent nucleotide" because the linker molecule separates the fluorophore from the nucleotide, and the oligonucleotide is often synthesized before the fluorophore-linker component is coupled to its 5′ terminal nucleotide. But all the "fluorescent nucleotides" disclosed by the patent involve coupling fluorophores to nucleotides—Promega identifies no other method of making a nucleotide fluorescent. And Promega's expert mentions no reason why the order in which the components are combined has any scientific effect on the end result. Promega has not asked me to construe the term "fluorescent nucleotide," and has proposed no intelligible definition

of the term that would exclude its product based on the separation between the nucleotide and the fluorophore-linker structure. So a fluorophore coupled to the terminal nucleotide constitutes a "fluorescent nucleotide."

Promega also challenges Life Tech's evidence that its products infringe. Claim 70 covers extension products—in this case the STR strands created during amplification—which "individually comprise a single fluorescent nucleotide." The use of the open-ended transitional phrase "comprising" signals that each STR strand must contain a single fluorescent nucleotide, though it contains additional components as well. *MagSil Corp. v. Hitachi Global Storage Technologies, Inc.*, 687 F.3d 1377, 1383–84 (Fed. Cir. 2012). The limitation excludes STR strands containing multiple fluorescent nucleotides, either as part of the initial oligonucleotide or added during chain extension. If STR strands with multiple fluorescent nucleotides were covered by claim 70, that claim would be indistinguishable from claim 62, and would violate the doctrine of claim differentiation that "two claims of a patent are presumptively of different scope." *Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1366 (Fed. Cir. 2000). Promega's expert has opined that certain Promega products label oligonucleotides use energy transfer dyes involving multiple fluorophores. Life Tech has not addressed which products employ multi-fluorophore labels, or whether any amplified STR chains contain multiple fluorescent nucleotides. Because of the remaining uncertainty as to the specific manner in which Promega's amplified STR chains are fluorescently labeled, I DENY Life Tech's motion for summary judgment of literal infringement of claim 70.

Finally, Life Tech has moved for partial summary judgment that Promega's representative product infringes claim 66 of the '096 patent. Claim 66 is independent of claim 62, and describes a composition created during the synthesis of DNA rather than a process for performing that synthesis. Claim 66 reads:

> 66. A mixture comprising a *polymerase* and a *duplex*, wherein the duplex comprises an *oligonucleotide specifically hybridized* to a *complementary strand of DNA*, wherein the *oligonucleotide* is covalently coupled to a *fluorophore* so as to allow chain extension by the polymerase.

The parties disputed the construction of the italicized terms, and I have rejected Promega's specialized definitions in favor of Life Tech's broader definitions that comport with the commonly-understood meanings of each term in the industry.

Promega argues that there's no evidence establishing that the PowerPlex 16 HS System embodies every limitation of claim 66. But Life Tech's citations to the PowerPlex 16 HS System Technical Manual are sufficient. Promega provides, as part of the PowerPlex 16 HS System, the polymerase and tagged oligonucleotides. Given my claim construction, there's no dispute that the latter are "covalently coupled to fluorophores."

Following Promega's protocol, the tagged oligonucleotides will bind to specific loci on the DNA strand that is to be analyzed and the polymerase will extend the bound oligonucleotide to create a copy of desired STR region. Repetition of the process will result in multiple amplified STR strands, each of which is a duplex. Life Tech's proffered evidence supports a finding that the mixture created after the polymerase chain extension has completed but before the amplified duplexes are denatured embodies the composition of claim 66, and Promega's arguments to the contrary all depend on claim constructions which I have rejected. I therefore GRANT partial summary judgment that the PowerPlex 16 HS System literally infringes claim 66 of the '096 patent.

Reissue recapture

The parties also seek summary judgment as to whether the '096 patent is invalid under the doctrine of reissue recapture. Reissue allows an inventor to amend a patent that has already been granted to correct an error in drafting, including "an attorney's failure to appreciate the full scope of the invention." *Medtronic, Inc. v. Guidant Corp.*, 465 F.3d 1360, 1375 (Fed. Cir. 2006). An inventor may use the process to broaden the claims in the patent if, "through error without any deceptive intention," he "claim[ed] … less than he had a right to claim in the patent." 35 U.S.C. § 251(a). A broadening reissue is only permitted "within two years from the grant of the original patent." 35 U.S.C. § 251(d), and does not extend the patent term—the reissued patent is valid only for "the unexpired part of the term of the original patent." 35 U.S.C. § 251(a).

The doctrine of reissue recapture "bars a patentee from recapturing subject matter, through reissue, that the patentee intentionally surrendered during the original prosecution in order to overcome prior art and obtain a valid patent," *In re Youman*, 679 F.3d 1335, 1343 (Fed. Cir. 2012), because in such circumstances the failure to claim the surrendered subject matter "cannot be said to involve the inadvertence or mistake contemplated by 35 U.S.C. § 251." *MBO Laboratories, Inc. v. Becton, Dickinson & Co.*, 602 F.3d 1306, 1313 (Fed. Cir. 2010). An inventor surrenders subject matter if, during patent prosecution, he "clearly and unmistakably argue[s] that his invention does not cover certain subject matter to overcome an examiner's rejection based on prior art." *Id.* at 1314. The question on summary judgment is whether the inventors clearly and unmistakably argued that their invention does not cover methods of nucleic acid sequence analysis other than DNA sequencing. Answering that question requires me to review the patent prosecution history.

In 1984, the inventors made a breakthrough in biochemistry by developing a way to attach a fluorescent tag to a DNA strand without preventing that strand from extending during replication. At the time, the sole known use of the method was in DNA sequencing, so the inventors drafted patent claims specific to DNA sequencing—for example, claims 1–12 of the original patent application (Application No. 06/570,973),

which claimed improvements to the chain degradation and chain termination sequencing methods. But before the patent issued, other uses of the method were developed. An inventor "is entitled to the benefit of all the uses to which [his invention] can be put, no matter whether he had conceived the idea of the use or not," *Roberts v. Ryer*, 91 U.S. 150, 157 (1875), and so the inventors amended their claims to include uses related to other types of nucleic acid sequence analysis. By at least 1992, as I noted earlier, it was clear to the examiner that the claimed invention was not limited to DNA sequencing.

When the original patent (U.S. Patent No. 6,200,748) was finally granted in 2001, many of the allowed claims made no mention of DNA sequencing. Life Tech's predecessor to the patent rights, Applera, sued Promega for infringement. See *Promega Corp. v. Applera Corp.*, 01-C-244-C, 2002 WL 32355680 (W.D. Wis. Jan. 2, 2002). During claim construction, Applera argued that two terms in the patent claims—"primer" and "template"—should be given their ordinary scientific meanings, while Promega argued, as it has here, for narrower constructions that would effectively limit the patent's reach to DNA sequencing. Judge Crabb sided with Promega, holding that the inventors "chose to be their own lexicographers" by including specific definitions of the terms "primer" and "template" in the patent specifications. *Id.* at *10, *14. The parties settled (perhaps to avoid a final judgment that would give that claim construction preclusive effect, e.g., *Talmage v. Harris*, 486 F.3d 968, 974 (7th Cir. 2007)), agreeing to cross-license patents that each side had asserted in the litigation, and in 2003 the inventors filed a reissue application to amend their claims.

The inventors' inadvertent error in the '748 patent was to use the terms "primer" and "template"—terms that they had defined narrowly in the specifications. Had they anticipated Judge Crabb's narrow construction during prosecution of the '748 patent, they would have known that they were claiming less than they were entitled to claim, and would have been entitled to amend the claims to use more general terms such as "oligonucleotide" and "complementary strand," as they later did in the reissued patent. Since this error did not become apparent until after the '748 was issued and was subsequently construed, they were entitled to fix it through the reissue process.

Promega argues that, by tying the scope of their invention to DNA sequencing in order to overcome prior art cited by the patent examiner during prosecution, the inventors surrendered all other methods of nucleic acid sequence analysis. But none of the prior art cited during prosecution involved nucleic acid sequence analysis. The examiner instead questioned whether the invention was obvious in light of four pieces of prior art: the chain degradation and chain termination methods of DNA sequencing; the "Kaplan" patent (U.S. Patent No. 4,151,065), which taught separating DNA strands by length using a process called "electrophoresis" and detecting the separated material using ultraviolet light; and the "Khanna" patent (U.S. Patent No. 4,318,846), which taught fluorescently tagging a DNA strand. None of these references made it possible to

extend a fluorescently tagged DNA strand and thus enable the use of fluorescent tagging in any method of nucleic acid sequence analysis, including DNA sequencing. The inventors made this clear during prosecution, stating for example that none of the cited prior art was "at all pertinent to the present invention and suggest nothing at all in relation to DNA sequencing." There is no clear statement in the record that the inventors intended to surrender methods of nucleic acid sequence analysis other than DNA sequencing. Even if their statements could be misunderstood to limit their claims to DNA sequencing, they quickly corrected this misapprehension, long before the '748 patent issued, and thus renounced any benefit from narrowing the scope of their invention.

Life Tech's motion to grant summary judgment that Promega has failed to meet its burden as to the doctrine of reissue recapture is therefore GRANTED, and Promega's contrary motion is DENIED.

Patent Prosecution Laches

Promega seeks summary judgment that laches bars Life Tech's claim of infringement because the patent's inventors were responsible for an "unreasonable and unexplained delay in prosecution," to Promega's prejudice. *Symbol Technologies, Inc. v. Lemelson Medical, Education & Research Foundation*, 422 F.3d 1378, 1384–86 (Fed. Cir. 2005). The patent prosecution history in this case is long–the original '748 patent issued in 2001, seventeen years after the initial 1984 application and during that seventeen-year period the inventors requested, and were granted, numerous extensions of PTO filing deadlines. However, Promega has not shown that the inventors deliberately delayed prosecution, either to enable Life Tech to capture later-developed technology or to extend the term of the patent. Nor has Promega shown that any of the delays were unreasonable.

Promega argues that the inventors unreasonably delayed issuance by abandoning Continuation Application Nos. 07/660,160 (Feb. 21, 1991) and 07/898,019 (June 21, 1992) even though each of those applications include claims that had been allowed by the patent examiner. "Refiling an application solely containing previously-allowed claims" "can be considered an abuse of the patent system," (the key word is "solely") but only if the refiling was "for the business purpose of delaying" the patent. *Symbol Technologies, Inc. v. Lemelson Medical, Education & Research Foundation*, *supra*, 422 F.3d at 1385. The '160 and '019 applications were continued in order to pursue claims that had been rejected and to add new claims; there is no showing that the continuations were filed for delay. And these two continuations account for just a handful of the many years of the prosecution history—hardly the "egregious case of misuse of the statutory patent system" required for prosecution laches. *Id.* at 1385.

Nor has Promega proved prejudice; it cannot explain what it would have done differently if the patent had issued earlier, or how it relied on, or was harmed by, the

delay. Promega raises the specter that long patent prosecutions will hide inventions from the public, slowing scientific progress. But that did not occur here; subject to some exceptions, patent applications are published 18 months after filing, see 37 C.F.R. § 1.211, and in this case, the invention was described, at least in part, in published scholarship as early as 1986. See Erich Strauss, et al., "Specific-Primer-Directed DNA Sequencing," 154 *Analytical Biochemistry* 353 (1986). No one disputes that the invention gained widespread use in the genetic analysis industry despite the delay. Promega's motion for summary judgment as to the defense of laches is therefore DENIED.

Priority Date

Life Tech has moved for summary judgment that the '096 patent has a priority date of January 16, 1984, which Promega challenges under the requirements of co-pendency and enablement. A patent can claim the priority date of an earlier patent application only if (1) the earlier application disclosed the same invention; (2) at least one inventor is common to both applications; (3) the later application specifically refers to the prior application, and (4) the current application was filed before the prior application was patented or abandoned. 35 U.S.C. § 120 (1988). The PTO approved the '096 patent as a continuation of a series of patent applications dating back to the original '973 application, filed January 16, 1984. The date of the patent is presumed correct, unless Promega can prove otherwise. *Technology Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1330–31 (Fed. Cir. 2008).

Promega alleges that there was a break in the co-pendency of the chain of applications when one of the applications from which Life Tech claims priority, Application No. 07/106,232, was abandoned on February 20, 1991, one day before the next application in the chain (the '160 application, filed February 21). If so, the two applications were not pending at the same time, and the '096 patent cannot claim priority prior to February 21, 1991. But the argument is waived because it was not presented in Promega's Invalidity and Unenforceability Contentions, which raise specific challenges to the priority date but say nothing about 1991 or the co-pendency rule; and Promega has not moved to update those contentions. See, e.g. *McDavid Knee Guard, Inc. v. Nike USA, Inc.*, 809 F. Supp. 2d 863, 878 (N.D. Ill. 2011).

Even if the issue was not waived, Promega's argument fails because there is no gap in co-pendency. The '232 application was abandoned when the inventors failed to file an appellate brief within two months of their notice of appeal. 37 C.F.R. §§ 1.192, 1.197 (1991); Manual of Patent Examining Procedures (MPEP), § 1215.04 (5th ed., revision 13, 1989) (the manual in effect at the time of the alleged break in co-pendency), www.uspto.gov/web/offices/pac/mpep/old/index.htm. The parties agree that under 37 C.F.R. § 1.8 the brief deadline runs from the date when the PTO *receives* an effective notice of appeal. The inventors' notice of appeal was due September 19, 1990, but was filed late, and so did not become effective until December 24, 1990, when the PTO

received a Request for an Extension of Time, MPEP, *supra*, § 1205, triggering a deadline of February 25, 1991 to file an appellate brief. The '160 continuation patent was timely filed four days before that deadline lapsed and rendered the '232 patent abandoned.

Moreover, the gap was at most a single day and could not have prejudiced anyone. The fate of protection for intellectual property protection for a major DNA invention should not be allowed to turn on a slip of scheduling of a single day, over twenty years ago. Cf. *Aristocrat Technologies Australia PTY Ltd. v. Int'l Game Technology*, 543 F.3d 657, 663 (Fed. Cir. 2008). These arguments have been made to the PTO, yet it still issued the patent and credits the 1984 priority date. I do not disagree.

Because I find for Life Tech on waiver and date of abandonment, I do not reach Life Tech's other arguments that may cure the alleged gap in co-pendency, such as whether there were still claims pending after February 25, 1991 from the '232 application and whether priority can be traced through the application 07/558,312.

Promega also argues that Life Tech cannot claim priority based on its earliest applications because those applications did not enable a person of ordinary skill in the art to practice the invention. A patent can only claim priority from an earlier application if the earlier application disclosed the claimed invention in accordance with 35 U.S.C. § 112. 35 U.S.C. § 120 (1988). The '096 patent specification discloses that the invention can be practiced by fluorescently tagging primers that meet four specific criteria,: "1) They must have a free 3' hydroxyl group to allow chain extension by the polymerase. 2) They must be complementary to a unique region 3' of the cloned insert. 3) They must be sufficiently long to hybridize to form a unique, stable duplex. 4) The chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase." It teaches that "one such primer is the 15-mer 5' CCC AG TCA CGA CGTT 3'." Patent No. RE43,096, Col. 5–6. Earlier patent applications disclosed merely the use of a 12-mer primer, or a 15-mer primer without mentioning the conditions. Application Nos. 06/570,973 (Jan. 16, 1983); 06/689,013 (Jan. 2, 1985); 06/722,742 (Apr. 11, 1985).

Promega alleges that neither the 12-mer primer disclosed in the '973 application, nor a 15-mer that doesn't meet the four criteria for a primer, can be used in DNA sequencing, and thus that the application would not enable a biochemist to practice the invention in a useful way without undue experimentation. Promega points to some of the inventor's contemporaneous notes that suggest that 12-mer primers produced unsatisfactory results; a contemporaneous article from another inventor, which concludes that there were problems with the DNA tests using the 12-mer primer, Erich Strauss, et al., "Specific-Primer-Directed DNA Sequencing," 154 *Analytical Biochemistry* 353 (1986); and at least one expert who concludes that the early applications did not enable the invention, in part because there were problems with the 12-mer primer.

Life Tech responds only that by 1984 scientists were doing DNA analysis with 12-mer primers, admittedly with radioactive rather than fluorescent tags, and that the

lab notes are inconclusive. Promega has therefore raised a question of material fact as to which patent application first enabled the invention. Life Tech's motion for summary judgment as to the priority date of the '096 patent is DENIED.

Breach of the 2006 Cross-License Agreement

Promega and Life Tech's predecessor agreed in 2006 to cross-license each others' patents so that both could sell products that perform genetic identity analysis, such as paternity testing and forensic DNA identification. Life Tech has demanded royalties from Promega for its use of the '096 patent and contends that Promega breached the 2006 cross-license agreement by refusing to pay.

The agreement obliges Promega to pay Life Tech 2% of its net sales of all "Licensed Products" from the date that Life Tech obtained a reissue of its '748 patent, which occurred on Jan. 10, 2012 when the '096 patent was granted. Life Tech's claim thus turns on which, if any, of Promega's products are "Licensed Products," defined in the agreement as "any product ... the manufacture, import, use, offer for sale or sale of which, but for the license granted in ... this Agreement would ... infringe at least one Valid Claim of any [Life Tech] patent." This definition, combined with the agreement's emphatic disclaimer that "NOTHING CONTAINED IN THIS AGREEMENT WILL BE CONSTRUED AS … AN ADMISSION BY EITHER PARTY THAT ANY OF ITS PRODUCTS INFRINGE ANY PATENTS OF THE OTHER PARTY" (capitalization in original), effectively requires an outside determination of which products infringe. I have made that determination by granting Life Tech's motions for summary judgment of infringement of claims 62, 63, and 66.

Promega argues that Life Tech's contract claim must be postponed until after all validity challenges to the '096 are adjudicated, on the theory that an invalid patent cannot be infringed and the scope of Promega's "Licensed Products" still cannot be determined until the patent's validity is established. That may be true as a matter of patent law (but see *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1583 (Fed. Cir. 1983) ("though an invalid claim cannot give rise to liability for infringement, whether it is infringed is an entirely separate question capable of determination without regard to its invalidity")), but this is a contract dispute. The agreement defines "Valid Claim" as "a claim of an issued patent that ... has not been held permanently invalid or otherwise unenforceable by a court of competent jurisdiction in a final and unappealable or unappealed ... judgment." Claims 62, 63, and 66 of the '096 patent meet this definition of "Valid Claim."

Finally, Promega notes that the cross-license agreement provides each side with a 30-day period within which to cure any material breaches, and the period is tolled during the pendency of litigation. But the cure period and tolling provision limit only a party's right to terminate the agreement; Life Tech is seeking to enforce it, not terminate

it. The provisions do not toll the parties' contractual obligations, and they do not suspend any determination of breach or damages, as Promega contends.

Promega's DNA fingerprinting products infringe claims 62, 63, and 66 of the '096 patent. All of the claims are "Valid" as defined in the cross-license agreement. Promega, therefore, is obliged to pay 2% of their net sales revenue as royalties, and its failure to do so constitutes breach. Life Tech's motion for summary judgment that it has breached the cross-license agreement is GRANTED.

United States Circuit Judge

April 4, 2013

TAB 2

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS EASTERN DIVISION

PROMEGA CORPORATION,	)	
	)	No. 13-cv-2333
Plaintiff,	)	
v.	)	Judge Richard A. Posner
	)	
APPLIED BIOSYSTEMS, LLC.,	)	
LIFE TECHOLOGIES CORP., and	)	
CALIFORNIA INSTITUTE	)	
OF TECHNOLOGY,	)	
Defendants.	)	

ORDER OF MAY 27, 2013

POSNER, *Circuit Judge*, sitting by designation. I conducted *Daubert* hearings on May 22–24, 2013, to consider challenges, based on Fed. R. Evid. 702 and pertinent judicial decisions, to the expert opinions offered in support of the parties' liability and damages theories. At the *Daubert* hearings I both heard arguments from the attorneys and questioned the experts (with one exception, because he had not yet been deposed—Jerry Ruth).

Life Technologies' Experts

*Carl Batt***.** Promega did not challenge Dr. Batt and my interchange with him at the *Daubert* hearing persuades me that he is qualified to provide relevant expert testimony.

Norman Dovichi. A professor of biochemistry, Dr. Dovichi opines that various prior art references published in the 1980s do not anticipate the '096 patent claims or render them obvious. He is qualified to opine on these issues.

Promega challenges his opining on secondary considerations of non-obviousness—evidence that the research and business community responded quickly and positively to the invention, suggesting that it was not obvious. (Had the invention, though valuable, as indicated by the business community's reaction, been obvious, presumably it would have been made earlier.) Dovichi says his "understanding" is that Life Tech and Promega each receive "significant revenue" from products covered by the '096

patents, but he does not support this claim or attempt to determine how much of the revenue is attributable to the patents; nor has he the expertise in economics or accounting that would enable him to make such a detrmination.

He also opines that "the fact that Promega have [*sic*] been selling products that are covered by the '096 patent is evidence that others have been copying the invention." That's a non sequitur. If the claims are obvious, Promega could have based its products on the prior art without copying Life Tech's products. I conclude that he is not qualified to testify about commercial success or copying of products based on the patent.

Dovichi attempts to bolster his contention of obviousness by claiming that the Smith 1986 paper, a paper in which the inventors of the '096 patent reported their research, was widely praised, suggesting that the advance made by the invention over the prior art was significant. But his only evidence is that the Smith 1986 paper has been cited 983 times. He offers no evidence that this is an unusually high number of citations for papers dealing with the pertinent aspects of DNA analysis, or that the citations are on balance positive. Citations can be negative as well as positive, and while Dovichi remarked dismissively at the Daubert hearing that of course he had not read all the articles that have cited the Smith paper, he could have read a random sample of them and did not. He also does not address whether praise for the Smith 1986 paper is an adequate proxy for praise for the patent. The contents of the paper do not overlap completely with the patent, and some citations may have been to features of the paper that do not appear in the asserted claims.. Dovichi may testify about the reputation of the inventors and the response of the biochemistry community to the invention itself, but may not offer analysis based on the response to the Smith 1986 paper.

Jed Greene. Mr. Greene is Life Tech's witness on damages. The 2006 cross-license between Promega and a Life Tech subsidiary specified a 2 percent royalty on sales of Promega products in the "Genetic Identity" field (primarily forensic analysis and paternity testing). Greene's report calculates the sales covered by the 2006 cross-license from internal data of Promega that categorize customers by field of use, and the sales outside of the Genetic Identity field (that is, sales outside the "field of use" of the 2006 cross-license) as well, because the latter sales constitute the base to which to apply a reasonable royalty in order to determine Life Tech's damages should Life Tech prevail on liability. Although Promega challenges Greene's decision to treat world-wide sales as infringing (should liability be found), the parties have not briefed the legal issues concerning the geographic scope of infringement, so I will not attempt to resolve them here. Greene may testify to the dollar amount of the sales to which, if infringement is found, a royalty rate may be applied, subject to my ruling on geographic scope.

Greene opines that a reasonable royalty rate would be 10 percent. Promega moves to exclude his opinion on the grounds that he fails to justify his conclusion, in part by ignoring the 2006 cross-license and failing to determine the value of Promega's products that is attributable to the patented technology.

Greene read 20 intellectual property licenses entered into by either Life Tech or Promega. The royalty rates ranged from 3 to 15 percent. He decided to narrow the range to between 7.5 and 15 percent based on six licenses that he claims are the ones most relevant to the '096 patent, then further narrowed it to between 8 and 12 percent without explanation before finally settling on 10 percent, the midpoint of that range, as his opinion of a reasonable royalty for sales of infringing products outside the field of use. His report does not identify the six licenses he relied on or explain why they were the most relevant, and he could not identify them at the *Daubert* hearing.

Some of the license agreements from which he derives his 10 percent estimate of a reasonable royalty license a predecessor to the '096 patent and any "continuations" (which would include the '096 patent itself), but license it or them for applications that may not relate to the specific patent claims at issue in this case. Moreover, each of the licenses covers multiple patents, not just the '096 patent and its predecessor, and Greene has not determined what percentage of the royalty rates in these licenses is attributable to the patent. Using the midpoint of a range of royalty rates in disparate licenses for unknown different inventions as the estimate of a reasonable royalty for a license for Promega products outside the field of use of the 2006 patent is arbitrary. See *Wordtech Systems, Inc v. Integrated Networks Solutions, Inc.*, 609 F.3d 1308, 1320 (Fed. Cir. 2010) ("comparisons of past patent licenses to the infringement must account for 'the technological and economic differences' between them"); *Lucent Technologies, Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1325 (Fed. Cir. 2009) ("licenses relied on by the patentee in proving damages [must be] sufficiently comparable to the hypothetical license at issue in suit"). At the *Daubert* hearing, as at his deposition, Greene testified simply that he considered the totality of the circumstances. But generalized impressions are no substitute for a method of computing, and evidence justifying, a reasonable royalty rate.

He might instead have started from the 2 percent royalty rate in the cross-license, identified likely differences between the 2006 negotiations and a hypothetical 2012 negotiation for a royalty for sales outside the field of use, and attempted to quantify the impact of these differences. He does note, for example, that the development of the stem cell market might have made the patent more valuable outside the Genetic Identity field in 2012 than it had been in 2006, but he offers no estimate of how much more valuable. And though he discusses Promega's high profit margin on the allegedly infringing products and argues that there are no commercially viable non-infringing alternatives to which Promega might have turned had it realized it was infringing a valid patent, he

offers no estimate of the profits that Promega would have lost had it not obtained a license and had ceased selling the products in question outside the field of use, or the share of those otherwise-lost profits that Life Tech could have extracted in negotiating a license. He did none of these things and so cannot be permitted to testify to a reasonable royalty rate.

Promega's Experts

Randall Dimond. Dr. Dimond is Promega's Chief Technical Officer. His expert reports opine that Promega's products do not infringe the '096 patent because they do not involve a method of nucleic acid sequence analysis or an oligonucleotide specifically hybridized (that is, matched) to a complementary DNA strand. He also identifies several non-infringing alternatives that Promega could have used instead of the fluorescent tags disclosed by the patent. In addition to the expert testimony contained in his report, Dimond intends to testify as a lay witness about Promega's products and license negotiations, matters he learned about through his job at Promega.

Life Tech asks me to bar Dimond from testifying in a dual capacity as both expert and lay witness. It argues that such testimony will confuse a jury, which will have difficulty separating Dimond's fact testimony from his expert opinions and will therefore give excessive weight to testimony unrelated to his expertise. In response, Promega offers to separate Dr. Dimond's trial testimony into two separate portions, first as a lay witness and then as an expert witness. But "telling the jury that a witness is both a lay witness *and* an expert witness and will be alternating between the two roles is potentially confusing—and unnecessary. The lawyer examining the witness need only ask him the basis for his answer to a question." *United States v. Moreland*, 703 F.3d 976, 983 (7th Cir. 2012). Hence I reject Life Tech's motion to exclude Dimond by virtue of the dual capacity in which he'll be testifying. Life Tech further argues that Dimond is biased because he has a stake in the suit's outcome as an employee and shareholder of Promega, but this is an issue that a jury can understand and give the proper weight to.

Where Dimond goes off the rails, and will not be permitted to offer testimony, concerns the issue of "specific hybridization." A molecule is specifically hybridized when it is designed to bind to a particular DNA sequence, which is the initial step making the multiple copies of the target DNA strand that are necessary for scientific instruments to be able to measure the strands. (They are measured by use of an electric field to pull them across a gel medium. Shorter strands move faster, and measuring the strand's location after a set time interval indicates its length. Although each copy of the target DNA will be tagged with one fluorescent molecule, indicating its position in the gel, a single flurophore is too weak to be detected in the gel, so multiple fluorescently-

tagged copies are necessary.) Claims 62 and 66 of the '096 patent involve oligonucleotides "specifically hybridized to the complementary strand of DNA." I construed the term in my claims-construction ruling to cover oligonucleotides (DNA molecules) "hybridized to a specific locus [i.e., location] on the complementary strand of DNA, even if that that locus is not unique." Promega had argued that its oligonucleotides are not specifically hybridized (hence don't infringe) because each can bind to more than one site in a DNA sample. I rejected this argument, ruling that oligonucleotides "engineered to hybridize to specific locations in a DNA sample" are "specifically hybridized" within the meaning of the patent even if they "can potentially bind to multiple loci on human genomic DNA." Dimond now concedes that this is correct if the oligonucleotides bind to multiple "related" sites, but he argues that Promega's oligonucleotides aren't specifically hybridized because each one may bind to unrelated sites on a DNA strand. This distinction between related sites (repetitions of the same gene at different locations in the human genome that share a common evolutionary origin) and unrelated sites (chance repetitions of the same nucleotide sequence) has no basis in either the patent or my claim construction. I explained that the patent never requires that the oligonucleotide bind solely to a single nucleotide sequence, as long as it's designed with a specific target in mind. Dimond's proposed opinion testimony about specific hybridization is irrelevant to infringement, and so will not be permitted. See Fed. R. Evid. 402, 702; *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 591–92 (1993).

Stephen Kent. Dr. Kent was a Senior Research Associate at Caltech from February 1983 to June 1989, a period that includes at least part of the time during which the research that culminated in the '096 patent, filed in January 1984, was conducted. He opines that Life Tech's claims for a "method of nucleic sequence analysis" (which I defined in my claims construction as "any method of obtaining information about a genetic sequence") are invalid because the patent's written description of the invention does not disclose any such method other than DNA sequencing (determining the identity and order of each and every nucleotide in a DNA sequence) and therefore does not show that the scope of the patented invention is as broad as claimed in the patent.

Kent relies primarily for his opinion on his personal observations of the activities performed by Caltech researchers during his time there—more than thirty years ago. Promega's lawyers could not explain at the *Daubert* hearing why personal recollections are relevant to the adequacy of a patent's written description, which depends only on whether it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Kent may not testify to those

activities or to his recollections of them. My ground is lack of relevance but I add that I am distrustful of the accuracy of recollections that are more than thirty years old, lack any confirmation in notes or other written or otherwise recorded materials or in the recollections of other persons, and are likely to be colored by what the recollector has learned since (hindsight bias).

Kent further claims, however, that his more than thirty-year-old experience at Caltech makes him a person of ordinary skill in the art at the time of the invention, qualifying him to opine on what the specification would have conveyed to one skilled in the art at that time. But his opening report does not discuss the adequacy of the specification, and his supplemental report, rather than filling that gap, focuses on his recollections of the activities of the Caltech researchers who invented the '096. The recollections that he emphasizes are that he was "not aware of any method of nucleic acid sequence analysis—other than DNA sequencing—routinely performed in the Hood Lab [of Caltech] as of January 16, 1984" and that "none of the inventors were in possession of PCR [Polymerase Chain Reaction." These observations are irrelevant to the adequacy of the written description or to how a person of ordinary skill in the art would understand it.

Fed. R. Civ. P. 26(a)(2)(B)(i) requires that all testifying experts submit "a complete statement of all opinions the witness will express and the basis and reasons for them." Kent's reports do not contain anywhere near a complete statement of his opinion on the adequacy of the specification in the '096 patent (the only issue about which he seeks to be permitted to testify).

Brian Van Ness. Dr. Van Ness, a professor of biochemistry, opines that the priority date of the '096 patent is subsequent to January 16, 1984 (the date claimed by Life Tech- the date the patent application was filed), because the patent application filed on that date does not enable the claims to be practiced or provide an adequate written description. In particular, he opines that the particular "12-mer" oligonucleotide described in the 1984 application could not properly hybridize to a complementary strand of DNA, as the patent requires. According to the inventors' lab notes, the 12-mer sometimes resulted in a "weak" or "smeary" signal in the inventors' tests before and after the filing of the application. Van Ness is qualified to assess the inventors' lab notes, and may opine that the priority date is later than 1984.

Like Dimond, however, Van Ness would also like to testify that Promega's oligonucleotides are not specifically hybridized. That is impermissible for the same reason that I am forbidding Dimond to give such testimony.

Nikos Panayotatos. Dr. Panayotatos, an independent consultant in biotechnology, seeks to demonstrate that the '882 (Ruth) patent (U.S. Patent No. 4,948,882, first filed in 1983), which like the '096 patent describes fluorescent tagging of DNA strands, either anticipates or renders obvious the claims of the '096 patent. He conducted an experiment to demonstrate that oligonucleotides tagged using the Ruth method are extendable (meaning that additional nucleotides, necessary for DNA replication and therefore for DNA analysis, can be attached to them). Panayotatos tested four oligonucleotides, each with the same DNA sequence, three of which were fluorescently tagged at different locations. All three variants were found to be extendable. While an experiment testing other sequences or tagging locations would have been desirable, Panayotatos's experiment provides some support for the argument that some or all of Ruth's oligonucleotides are extendable, and he may therefore testify about it. However, I warn that he was unresponsive when I asked him to explain the experiment in simple, lay terms that would be intelligible to jurors. The trial will be a jury trial. If he is unable to testify at a level intelligible to jurors, I will not permit him to testify at all.

Life Tech contends that Panayotatos's report does not adequately explain his conclusion that prior art references anticipate the '096 patent's claims or render them obvious. His report incorporates by reference an "invalidity claim chart" prepared by Promega's attorneys. The chart consists of excerpts from the Ruth patent and other citations, with no analysis. Experts may not merely rubber stamp a lawyer's argument. But Panayotatos's report also contains his own assessments of the Ruth patent, and he may testify to those—but only to those.

Life Tech further objects that although Panayotatos opines that the dependent claims of the '096 patent are invalid, he offers no support for that opinion other than his discussion of the independent claims. But that discussion provides some basis for his conclusions about the dependent claims, which contain many elements of the independent claims. He need not opine on all elements of the dependent claims in order to opine that some elements are obvious or anticipated. But he may not offer testimony on claim elements not discussed in his report.

Finally, Life Tech objects to Panayotatos's testimony about the degree of experience that a person of ordinary skill in the art would possess, but his experience in the biochemistry field during the relevant time period qualifies him to opine on that issue.

Carl Degen. Mr. Degen is Promega's expert witness on damages. Degen opines that 80 percent of distributor sales are within the scope of the 2006 cross-license (and so are not a basis for damages in this case) because 80 percent of Promega's direct customer sales are within that scope. But he admits that neither he nor Promega has no information about what percentage of resales by distributors are within that scope and

so not a part of the royalty base for determining damages for infringement of the '096 patent. Hence he will not be permitted to testify that any distributor sales are covered by the cross-license. Degen also identifies sales to North American customers based on the sales-district field in Promega's customer data. Whether he can testify about those sales will depend on my legal determination of the geographic scope of infringement.

Subject to these exclusions, Degen may testify about the proper royalty base.

As to royalty rate, Degen concedes that a reasonable royalty for a license for Promega products outside the field of use of the 2006 cross-license would be 2 percent or perhaps slightly higher. I take this to be a concession by Promega that if it is determined to have infringed the '096 patent, Life Tech is entitled to a 2 percent royalty. Since I am not permitting Jed Greene, Life Tech's only expert witness on damages, to testify as to royalty rate, I don't see what relevance (given the concession) Degen's testimony would have with regard to that rate. A concession doesn't require a witness.

In many cases lay as distinct from expert evidence is adequate for calculating damages, but I don't see how that could be so when one is dealing with so complex a technology as involved in this case. If last year Promega had admitted infringement, the royalty that Life Tech could have extracted from it would have depended primarily on Promega's alternatives, rather than on the terms of other licenses, including the 2006 cross-license. I see nothing in the parties' preparation of this case that provides a basis for a jury's assessing damages. Before I decide whether to allow Degen to testify, I want the parties to submit briefs clarifying their positions on damages and explaining what evidence they propose to present on damages given my exclusion of Greene's royalty rate opinion. My inclination at present is that the only basis for any award of damages is what I take to be Promega's 2 percent concession, and that it should be possible for the parties to stipulate, or for me to resolve on summary judgment, the royalty base and hence remove the damages issue from the trial entirely. These briefs shall be due on May 31 and if the parties prefer can be incorporated as part of the summary judgment briefs they'll be filing that day.

United States Circuit Judge

May 27, 2013

TAB 3

UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

PROMEGA CORPORATION,	)	
	)	No. 13-cv-2333
Plaintiff,	)	
v.	)	Judge Richard A. Posner
	)	
APPLIED BIOSYSTEMS, LLC.,	)	
LIFE TECHOLOGIES CORP., and	)	
CALIFORNIA INSTITUTE	)	
OF TECHNOLOGY,	)	
Defendants.	)	

ORDER OF JUNE 4, 2013

Promega has moved to strike Life Tech's supplemental response to interrogatories [dkt. 411], which amends Life Tech's contention about the priority date of the '096 patent to suggest, for the first time, a priority date earlier than January 16, 1984, the date on which the patent application was filed. I grant the motion because Life Tech's supplemental response is foreclosed by its prior litigating positions in this lawsuit.

On September 25, 2012, Promega served interrogatories on Life Tech and Caltech requesting any information supporting a priority date for the asserted '096 patent claims earlier than the patent's filing date of January 16, 1984. Life Tech and Caltech responded one month later; each disclaimed knowledge of any information supporting an earlier date, despite an affidavit sworn by Lloyd Smith, an inventor of the '096 patent, that Life Tech now contends shows that he both conceived of the invention and reduced it to practice in 1982 or 1983. Promega referred to the Smith affidavit in filings in this litigation as early as June 2012 [dkt. 217-7 at pp. 31–33], but Life Tech's interrogatory contentions failed to disclose its intention to rely on the affidavit to argue for a priority date earlier than 1984. Life Tech's subsequent summary judgment motion stuck to the position "that the '096 patent is entitled to its stated January 16, 1984 priority date," again with no mention of any earlier date. [dkt. 211 at p.53].

Life Tech and Caltech were obligated to amend their interrogatory responses "in a timely manner" after obtaining information contradicting their earlier interrogatory response, if they wanted to change their earlier response. Fed. R. Civ. P. 26(e)(1)(A). Life Tech offers no explanation for its having delayed the attempt to amend until literally two minutes before the close of discovery. It argues only that Promega wasn't prejudiced by it. But Promega was prejudiced. Had it known of Life Tech's intention to rely on the affidavit to support an earlier priority date, Promega might have directed its experts to opine on the adequacy of the evidence that Smith in fact conceived of the '096 invention and reduced it to practice before 1984.

Life Tech's slipshod belatedness is inexcusable. I hereby strike Life Tech's supplemental interrogatory responses and forbid it to argue for a priority date earlier than January 16, 1984.

United States Circuit Judge

June 4, 2013

TAB 4

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS

PROMEGA CORPORATION,	)	
Plaintiff,	)	No. 13-cv-2333
	)	
v.	)	Judge Richard A. Posner
	)	
APPLIED BIOSYSTEMS, LLC,	)	
LIFE TECHOLOGIES CORPORATION,	)	
and CALIFORNIA INSTITUTE OF	)	
TECHNOLOGY,	)	
Defendants.	)	

SECOND ORDER OF JUNE 5, 2013

At the summary judgment argument on June 7, the parties should be prepared to address whether the asserted claims of the '096 patent are rendered invalid by the Smith '800 patent under the doctrine of obviousness-type double patenting. See, e.g., *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013); U.S. Patent and Trademark Office, *Manual of Patent Examining Procedure* § 804. The parties shall submit supplemental briefs on the issue, due simultaneously at 9 p.m. (CDT) tomorrow, June 6.

Richard A. Posner

United States Circuit Judge

June 5, 2013

TAB 5

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS

PROMEGA CORPORATION, *Plaintiff*,	)	No. 13-cv-2333
v.	)	Judge Richard A. Posner
APPLIED BIOSYSTEMS, LLC, LIFE TECHOLOGIES CORPORATION, and CALIFORNIA INSTITUTE OF TECHNOLOGY, *Defendants.*	)	

OPINION OF JUNE 12, 2013

On June 7, 2013, I conducted a hearing to resolve a *Daubert* challenge to Dr. Jerry Ruth, and to hear argument on the motions by Promega and the defendants (whom I'll refer to collectively as Life Tech) for summary judgment on infringement, damages, and validity. On the basis of that hearing and the motions, I grant summary judgment that claims 62 (and claim 62's dependent claims), 66, and 67 of U.S. Patent No. RE43,096—the '096 patent that Promega challenges and Life Tech seeks to enforce—are invalid. These rulings require entry of judgment in favor of Promega; the judgment order will be issued as soon as this opinion is docketed. For completeness I also discuss in this opinion the summary judgment motions dealing with infringement and with damages.

Daubert challenge to Jerry Ruth.

Dr. Ruth, a highly-qualified biochemistry research scientist, has opined that the asserted claims of the '096 patent are invalid as anticipated by, or obvious in light of, prior art. Life Tech has moved to exclude his opinions and testimony on the authority of Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 591–92 (1993). Ruth's report emphasized a 1986 article in *Nature* coauthored by Lloyd Smith, one of the '096 inventors. But he now concedes that the article is not prior art, and therefore irrelevant, because it postdates the patent's priority date of January 16, 1984.

Life Tech challenges Ruth's analysis of other prior art, including U.S. Patent No. 5,118,800 (the "Smith '800 patent"), as hastily articulated, vague, and conclusory. That characterization is inaccurate; Ruth's report analyzes at length the prior art that Promega contends invalidates the '096 claims and describes the parts of those references

that he believes an ordinarily skilled biochemist would have known to combine in order to be able to practice the disputed claims of the '096 patent. So had this case gone to trial, Ruth would have been allowed to testify as an expert witness except with regard to Smith's article.

Infringement.

I can dispose of the infringement and damages issues very briefly and so will begin with them. Life Tech has moved for summary judgment that Promega's manufacture, testing, and sale of various products directly infringe claims 62, 66, and 67 of the '096 patent and that Promega is additionally liable for having induced its customers to infringe the same claims by using its products. See 35 U.S.C. §§ 271(a), (b), (f). Life Tech's submission at dkt. 397-1 outlines the specific products in question and the manner in which Life Tech contends that they infringe each claim. "To streamline the case so there will not be a dispute on infringement," Promega now concedes Life Tech's contentions regarding infringement with two reservations with which Life Tech doesn't quarrel. The first is that if only claim 62 is valid, Promega denies liability for inducing infringement by foreign customers, see 35 U.S.C. § 271(f), because that section does not cover method claims. *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348, 1359 (Fed. Cir. 2009) (en banc). Second, Promega's products that do not use four sets of fluorescent tags do not infringe claim 67. Those concessions resolve any disputes about infringement.

Damages.

Jed Greene, Life Tech's damages expert, wanted to testify that 10 percent would be the proper royalty rate applicable to sales of products found to infringe '096 if the relevant claims of the patent are valid. On the basis of Greene's testimony at the *Daubert* hearing, I ruled that he would not be allowed to testify about royalty rate. Carl Degen, Promega's damages expert, had in various places in his expert report, deposition, and *Daubert* testimony indicated that he thought the reasonable range for the royalty rate would be 2 to 4.4 percent. Life Tech asks me to treat this as a concession by Promega that 4.4 percent is a reasonable rate, and notes that the figure is derived in part from evidence given by Life Tech's chief technical officer, Randall Dimond.

I am sympathetic to the proposition that if a defendant concedes a reasonable range for a royalty rate, the plaintiff (if it proves liability) should be entitled to the top of the range if, as in this case, there is no evidence that would permit a jury to select a point within that range as being the most reasonable damages estimate. This approach would be consistent with case law that, while insisting that injury be proved in the usual way, permits doubts about the amount of damages to be, within reason (obviously an essential, and sometimes overlooked, qualification), resolved in the plaintiff's favor. See, e.g., *Story Parchment Co. v. Paterson Parchment Paper Co.*, 282 U.S. 555, 562–63 (1931); *Datascope*

Corp. v. SMEC, Inc., 879 F.2d 820, 826 n. 6 (Fed. Cir. 1989). This approach is appropriate because invariably the violation of the defendant's rights will have made an exact calculation of damages difficult and often impossible.

But I don't think Degen's testimony and proposed testimony considered as a whole constitute a concession that the reasonable royalty should be 4.4 percent; he also offers reasons why a jury could come to 2 percent. For while he indeed derived the 4.4 percent figure from Dimond's evidence of Promega's charging a higher royalty, he also expressed disagreement with Life Tech's interpretation of that evidence. That disagreement itself requires some explaining.

In 2006, Promega and Life Tech settled litigation over genetic-identity products that used technology patented by both companies. Promega agreed to pay Life Tech a 2 percent royalty for use of Life Tech's '096 patent if the patent was reissued (as it was); Life Tech agreed to pay a 5.5 percent royalty for use of Promega's STR ("short tandem repeat") patents; Life Tech promised to maintain the compatibility of its machines with Promega's products (chemicals used with those machines).

Dimond has testified that Promega's STR patents would have commanded a 12 percent royalty in a one-way license deal (he implies others had paid that rate) but had reduced the rate to 5.5 percent in exchange for Life Tech's promise to maintain its machines' compatibility with Promega's products. Degen likes this explanation of the discount because if that promise was responsible for the rate, no other terms of the 2006 agreement, including Life Tech's 2 percent royalty, would be affected. So Degen argues 2 percent would be the right royalty rate to expect the parties to have agreed on in 2012 with respect to Promega products outside the field of use governed by the 2006 cross-license.

Life Tech disagrees. Its position is that Promega accepted a lower rate in exchange for getting its own lower rate, implying that the 2 percent rate was also lower than Life Tech would grant in a single-license deal, that is, a deal in 2012 allowing Promega to use Life Tech's patent in Promega products outside the field of use of the 2006 license.

Degen's 4.4 percent calculation is a back up, lest the trier of fact think 2 percent too low, in which event Degen wants the trier to assume for argument's sake that in the cross-license negotiation in 2006 each party gave the other the same percentage discount. Promega discounted its normal 12 percent rate to 5.5 percent, a 54 percent discount, implying (given the assumption of identical discounts) that Life Tech accepted a 54 percent discount; and if 2 percent is a 54 percent discount from Life Tech's standalone royalty rate, that rate was 4.4 percent. But this as I said is Degen's (and Promega's) back-up position. His (and its) preferred interpretation is that the proper royalty damages rate is only 2 percent, and he could so testify were there a trial on damages, subject of course to cross examination of his testimony on his opinion, including the 4.4 percent alternative.

I want to discuss one more issue that in view of my analysis of validity is not dispositive:

"Specifically hybridized."

In order to preserve a record for appeal, Promega continues to press its challenge to the construction of the term "specifically hybridized" (i.e., designed to bind to) in my April 4 and May 27 orders, in which I construed the term to cover all oligonucleotides intended to bind to a specific location on a complementary strand of DNA even if that location is not unique. Promega argues that the term means "binding to one and only one location on a complementary strand of DNA."

Promega complains that it had no opportunity to brief construction of this claim term, but it could and should have made all the arguments it now seeks to make in earlier submissions. When Life Tech moved for summary judgment that Promega's Power Plex 16 HS system infringes the '096 patent, Promega argued that the Power Plex 16 HS system doesn't infringe because its oligonucleotides can bind to multiple sites on the complementary DNA strand and therefore aren't specifically hybridized, which Promega defines as meaning that the oligonucleotide must bind to a unique site. My ruling on that summary judgment motion required me to interpret the term, and I rejected Promega's construction. My prior orders explain why Promega's construction is unreasonably narrow.

Turning now to the dispositive issue, that of validity, I need to address a series of sub-issues, beginning with—

Anticipation, Obviousness, and Obviousness-Type Double Patenting.

Ordinarily the jury resolves all factual disputes relevant to validity, e.g. *SynQor, Inc. v. Artesyn Technologies, Inc.*, 709 F.3d 1365, 1373 (Fed. Cir. 2013), but if the facts are undisputed (in the sense either that the parties agree on the material facts, or that there could be no reasonable disagreement over what they are, given the record in the case), the judge decides the case, ordinarily on the basis of a motion for summary judgment. See, e.g., *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 427 (2007); *OSRAM Sylvania, Inc. v. American Induction Technologies, Inc.*, 701 F.3d 698, 704 (Fed. Cir. 2012); *MySpace Inc. v. GraphOn Corp.*, 672 F.3d 1250, 1257 (Fed. Cir. 2012).

Promega seeks summary judgment on the basis of the doctrines of anticipation and obviousness. In addition, I requested and received briefing on the claims' validity under the doctrine of obviousness-type double patenting.

Promega's arguments for anticipation and obviousness rely in large part on the '800 patent, which claims the chemical structure of a linker arm that can be used to attach a fluorophore to an oligonucleotide. The '800 patent shares a common inventor with the '096 patent, so Life Tech argues that it is not prior art, see 35 U.S.C. § 102(e)(2), and al-

ternatively that if it is prior art it may not be considered for purposes of determining obviousness. See 35 U.S.C. § 103(c)(3).

The Smith '800 Patent is Prior Art. Prior art includes "a patent granted on an application…*by another* filed…before the invention by the applicant." 35 U.S.C. § 102(e)(2) (2011) (emphasis added). The application leading to the issuance of the '800 patent (No. 06/565,010) was filed on December 20, 1983, one month before the application for the '096 patent.

If the inventors on two applications are different, then one patent is owned by one inventor and the other patent by the other inventor. *In re Kaplan*, 789 F.2d 1574, 1575 (Fed. Cir. 1986); *Application of Land*, 368 F.2d 866, 876–79 (C.C.P.A. 1966); 3 *Chisum on Patents* § 3.08(a) (2013). And if there are two inventors on one application and two other inventors on the other, each pair is the owner of one of the patents. Although Lloyd Smith is listed as an inventor of both the '096 and '800 patents, the '096 lists four additional inventors (Lee Hood, Michael Hunkapiller, Tim Hunkapiller, and Charles Connell); the '800 therefore belongs to "another" (that is, another inventing entity from the inventing entity of the '096) and thus can be prior art used to challenge the validity of the '096.

When research by a single research *team* results in multiple patent applications listing different inventors, the inventor of one of the patents can avoid having the patent applications from other inventors on their team treated as prior art by establishing an earlier priority date, and he can do by proving that he reduced his invention to practice before the patent application or applications filed by the other inventors. See, e.g., *Applied Materials, Inc. v. Gemini Research Corp.*, 835 F.2d 279, 281 (Fed. Cir. 1987). Thus, patent applications from related inventors avoid invalidating each other not through the "of another" requirement (for different inventors are always "another," or more precisely "others"), but through the rule that assigns a priority date based on when the invention was made rather than when the patent application was filed. Since the '800 and '096 patent applications were filed just one month apart, the technology patented in the '096 may have been invented before the '800 patent application was filed, which would prevent the '800 patent from being used as prior art to challenge the validity of the '096 patent even though the inventors were not identical.

But Life Tech has waived any argument for an earlier priority date for the '096. It moved for summary judgment that the priority date is January 16, 1984, [dkt. 211], which of course is after December 20, 1983; denied that there was any evidence of an earlier date in its interrogatory responses; and failed to amend those responses in timely fashion. See my Order of June 4, 2013, dkt. 437. The priority date of the '096 patent is therefore January 16, 1984, making the '800 patent prior art. 35 U.S.C. § 102(e).

The Smith '800 Patent Does not Qualify for the § 103(c) Safe Harbor. Prior art under section 102(e) that does not anticipate a patent claim may nonetheless render the claim obvious under 35 U.S.C. § 103. But there is a safe harbor, designed to encourage (or at least not penalize) team research, 35 U.S.C. § 103(c); *OddzOn Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1403 (Fed. Cir. 1997); *In re Longi*, 759 F.2d 887, 894 (Fed. Cir. 1985): an earlier patent application filed by another inventor, although prior art under section 102(e), will not render a later patent obvious if both patents were "owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. § 103(c)(1) (2012). "The statute is directed to situations of common ownership," *In re Hubbell*, 709 F.3d 1140, 1153 (Fed. Cir. 2013), and thus requires that both patents be "entirely or wholly owned by" or assigned (or contractually obliged to be assigned) to the same entity. Manual of Patent Examining Procedure § 706.02(l)(2)(I). "If the person(s) or organization(s) owned less than 100 percent of the subject matter which would otherwise be prior art to the claimed invention, or less than 100 percent of the claimed invention, then common ownership would not exist." *Id*.

Section 103(c) looks to the alleged patent owner's rights "at the time the claimed invention was made." 35 U.S.C. § 103(c)(1) (2012). Life Tech argues that as of January 16, 1984, Caltech was the sole owner of the patents. For before that date Smith had assigned the rights to the '800 patent to the university and the 1984 application that led to the '096 patent had four inventors originally, all of whom also assigned their rights to the university before January 16, 1984 [dkt. 468-2]. But the '096 patent had five inventors, for in 1988 Caltech had petitioned the PTO to add Charles Connell as an inventor, and the petition had been granted [dkt. 199-7, PROM008425-30]. The inventors listed on a patent must include everyone who contributed to and thus has legal rights in the invention, because you cannot patent material if you "did not [yourself] invent the subject matter sought to be patented," 35 U.S.C. § 102(f) (2004); *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1349 (Fed. Cir. 1998); 1-2 *Chisum on Patents* § 2.03 (2013) ("the originality requirement bars issuance of a patent to a person or persons who derive the conception of the invention from any other source or person"). Life Tech argued that Connell had contributed to the invention and therefore had to be added to the patent. But he didn't assign his patent rights to Caltech until 1988. Having conceded that Connell is a necessary inventor of the patent, Life Tech cannot now argue that Caltech had full ownership rights to the invention before Connell assigned his rights to the university in 1988.

Like many research institutions, Caltech has long required its employees to assign to it the rights to any invention made using university resources. "All employees are required to sign a patent agreement assigning their rights to inventions which they may make in the line of duty, on Institute time, or with Institute facilities to the Institute or its nominee." California Institute of Technology Staff Personnel Memoranda, Subject: Patent Policy, Section 2.a.(1) (1977) [dkt. 459]. But Connell was employed by Applied Biosystems, never by Caltech. Life Tech presents no evidence that he was required to

assign his rights to Caltech at the time of invention. And one month after filing the initial application for the '096 patent in February 1984, the university represented to the PTO that it shared ownership with Applied Biosystems. [dkt. 199-4, p. 39]. In sum, the university was not the sole owner of the patented invention at the time of invention. Section 103(c)(1) therefore does not apply.

It is true that under the version of § 103(c) in effect when the '096 patent was reissued, research stemming from "a joint research agreement that was in effect on or before the date the claimed invention was made" could nonetheless be "deemed to have been owned by the same person or subject to an obligation of assignment" when certain conditions were met. 35 U.S.C. § 103(c)(2) (2012). But "joint research agreement" is limited to "a written contract, grant, or cooperative agreement." 35 U.S.C. § 103(c)(3) (2012). Although Life Tech has proved that Caltech and Applied Biosystems collaborated during the 1980s—Lloyd Smith, for example, worked as an independent consultant for Applied Biosystems—it has not identified any written joint research agreement covering the invention, or argued that such a written agreement exists or ever existed. Because section 103(c) therefore does nothing for Life Tech, I do not reach Promega's argument that section 103(c) is inapplicable because the '096 patent stems from a patent application that dates back to 1984.

With 103(c) not applying, the '800 patent is prior art for both anticipation under § 102(e) and obviousness under § 103. I have now to consider whether either or both of these doctrines invalidate claims in the '096 patent.

Anticipation. Because the Smith '800 patent is prior art, it will anticipate—and therefore render invalid—a claim of the '096 patent if "each and every element as set forth in the claim is found, either expressly or inherently described" in its specification. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). An element is described if it "is necessarily present in the thing described in [a prior art] reference, and…would be so recognized by persons of ordinary skill." *Id.* Anticipation is a question of fact, but summary judgment is appropriate if there is no genuine dispute of material fact. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1327 (Fed. Cir. 2001).

The '800 patent describes the chemical structure of a linker arm and the use of that linker arm to attach a fluorophore to an oligonucleotide. (3:60–64; 5:50–51) It also describes the use of these fluorescently tagged oligonucleotides in DNA sequencing: "the synthesis of fluorescent-labeled oligonucleotides permits the automation of the DNA sequencing process" (3:64–68) and the labeled oligonucleotides "are effective in DNA hybridization methods, as illustrated by their use as primers in DNA sequence analysis." (5:51–55). Smith acknowledged at his deposition that these references to DNA sequencing describe the Sanger method. Smith deposition, May 28, 2013 (dkt. 392), at 151:26–154:10. The Sanger method was invented in 1977 as a way to perform DNA sequencing—determining the specific order of nucleotides in a target strand of DNA. A

known DNA sequence called a cloning vector is attached to the target strand. An oligonucleotide designed to bind to the cloning vector is tagged so that it will be detectable at a later stage in the sequencing. The oligonucleotide binds to the cloning vector, forming a "duplex"—a double-stranded DNA molecule. A chemical called a polymerase is introduced to catalyze the extension of the oligonucleotide along the complementary strand. Modified nucleotides associated with a particular nucleic acid base are added to the end of the strand to prevent additional nucleotides from binding. The result is strands of different lengths ending in a particular base; the lengths of the strands are then measured to determine the sequence of nucleotide bases in the target strand. A person skilled in the art would have recognized the reference to the Sanger method, would be familiar with the steps of that method, see Dovichi rebuttal report, Jan. 15, 2013 (dkt. 297), at ¶¶ 40–41, and would therefore understand those steps to be a necessary part of the '800 patent specification.

The Sanger method was widely used in the early 1980s. Dovichi deposition, May 6, 2013 (dkt. 392), at 137:9–12. At the time, oligonucleotides were tagged using radioactive labels, but these were expensive, required costly safety precautions, and could not be read reliably by a computer. It was widely understood that fluorescent tags ("fluorophores") would be preferable on all three counts (U.S. Patent No. 4,948,882 ("Ruth '882 patent") at 1:43–2:2). But fluorescent tags, unlike radioactive ones, might interfere with the chemical reactions in Sanger sequencing. The research leading to the '800 patent solved this problem: Smith and other Caltech researchers used a linker arm with a specific chemical structure to attach a fluorophore to the oligonucleotide in a way that didn't interfere with the binding and extension processes and that could therefore be used in the Sanger method.

In December 1983 Smith applied for a patent (the '800 patent) on the linker arm. The specification of this patent stated that the linker arm could attach a fluorophore to an oligonucleotide, which could then be used in the Sanger method (3:64–68; 5:51–55). In January 1984, Smith and others filed a second application, which became the '096 patent. This application described the use of an oligonucleotide tagged with the linker arm for use in the Sanger method. The '096 patent resulted from the same line of research as the '800 patent, and Promega contends that the asserted claims of the '096 are anticipated by the '800. I discuss those three claims in turn.

Claim 62 (and its dependent claims). In describing the use of fluorescently tagged oligonucleotides to perform Sanger sequencing, the '800 patent either expressly or inherently discloses every element of claim 62—which describes:

> A method of nucleic acid sequence analysis, comprising extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product, wherein the duplex comprises the oligonucleotide specifically hybridized to the complemen-

tary strand of DNA, and wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

The ‘800 patent discloses an “oligonucleotide…covalently coupled to a fluorophore.” Each of the claimed linker arms is a covalent coupling that can attach an oligonucleotide to a fluorophore (35:1–38:5). Each of the additional elements of the claim is inherently present in the Sanger method, in the sense that a person skilled in the art would understand the presence of those elements to be necessarily implied by the patent’s references to the use of the described oligonucleotides in DNA sequencing. Sanger sequencing is “a method of nucleic acid sequence analysis” that, as I have explained, necessarily involves “extending” the disclosed, fluorescently-tagged oligonucleotide “along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product, wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA.” And when a linker arm is used, it must necessarily “allow chain extension by the polymerase” in order to function effectively in Sanger sequencing. The resulting “extension product” will be “labeled” because of the attached fluorophore.

Life Tech disputes none of this. Asked at the summary judgment hearing to explain why the ‘096 patent represents an advance over the ‘800, it said only (so far as relates to claim 62) that the ‘096 patent contains “an example of actually generating sequence information by using the oligonucleotides.” But the ‘800 patent states that the oligonucleotides it describes “are effective” in sequencing, not that they could become so only after further research (5:51–55); and so the absence of an example from the specification of the ‘800 is irrelevant. Specifically, the oligonucleotides are “effective” by reason of their “use as primers in DNA sequence analysis” (*id*.). Life Tech’s brief says that the ‘800 patent “claims a fundamentally different invention” from the ‘096 patent, but the specification describes the use of the linker arms in Sanger sequencing, and that shows that the ’800 anticipates claim 62 of the ‘096.

Promega’s experts have not said that the ‘800 patent anticipates the ‘096 patent. But expert witnesses are not required, and normally are not expected, to offer legal conclusions. The experts’ reports discuss the relevant portions of the ‘800 patent and explain their overlap with the ’096, and that’s sufficient. Life Tech points out that claim 62 covers more than Sanger sequencing reactions that use the Smith ‘800 linker arm; it covers all methods of nucleic acid sequence analysis and all linker arms that allow the oligonucleotide to hybridize and extend. But a prior art reference that discloses a particular species anticipates the genus (in this case, all methods of nucleic acid sequence analysis) to which the species belongs. *In re Gosteli*, 872 F.2d 1008, 1010 (Fed. Cir. 1989); *In re Slayter*, 276 F.2d 408, 411 (C.C.P.A. 1960).

Promega argues that the ‘800 patent also anticipates the dependent claims of claim 62. Those claims are:

> 63. The method of claim 62, further comprising separating said labeled extension product from said duplex.
>
> 65. The method of claim 64 or claim 62, wherein the fluorophore is covalently coupled to the oligonucleotide through an amine linkage. [Life Tech appears to assert this claim only as a dependent claim of claim 62.]
>
> 70. The method of claim 62, wherein substantially all molecules of the labeled extension product individually comprise a single fluorescent nucleotide.
>
> 74. The method of claim 62, wherein substantially all molecules of the labeled extension product are individually coupled to a fluorophore by a single covalent linkage.
>
> 80. The method of claim 74, wherein substantially all molecules of the labeled extension product individually are terminally labeled with a fluorophore.
>
> 86. The method of claim 70, wherein substantially all molecules of the labeled extension product individually are terminally labeled with a fluorophore.
>
> 92. The method of claim 74, wherein substantially all molecules of the labeled extension product individually comprise a 5' terminal fluorescent nucleotide.
>
> 98. The method of claim 86, wherein substantially all molecules of the labeled extension product individually comprise a 5' terminal fluorescent nucleotide.

The additional elements of the claims dependent on claim 62 are also found in the '800 specification. Sanger sequencing requires that the labeled oligonucleotide be "separated" from the duplex (claim 63). The linker arms claimed in the '800 patent are amine linkages (claim 65), Dovichi rebuttal report, Jan. 15, 2013 (dkt. 297), at ¶ 93, and they connect a single fluorophore to a single nucleotide at the 5' terminal end of the oligonucleotide (claims 70, 74, 80, 86, 92, and 98). *Id*. Dovichi rebuttal report, Jan. 15, 2013 (dkt. 297), at ¶ 93. The dependent claims are therefore also anticipated.

Claim 66. Claim 66 describes:

> A mixture comprising a polymerase and a duplex, wherein the duplex comprises an oligonucleotide specifically hybridized to a complementary strand of DNA, wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

As I've already pointed out, the '800 patent discloses an "oligonucleotide…covalently coupled to a fluorophore," which would necessarily "allow chain extension by the polymerase" if used in Sanger sequencing. The remaining portion of claim 66—"a mixture comprising a polymerase and a duplex, wherein the duplex comprises an oligonucleotide specifically hybridized to a complementary strand of DNA"—is necessarily formed during Sanger sequencing. Claim 66 claims the mixture that results when a method of sequence analysis described in claim 62 is performed with a fluorescently tagged oligonucleotide, as the '800 patent instructs. Because the '800 patent either expressly or inherently discloses every limitation of claim 62, it discloses every limitation of claim 66 as well. Claim 66 is therefore anticipated by the '800 patent.

Claim 67. Claim 67 recites:

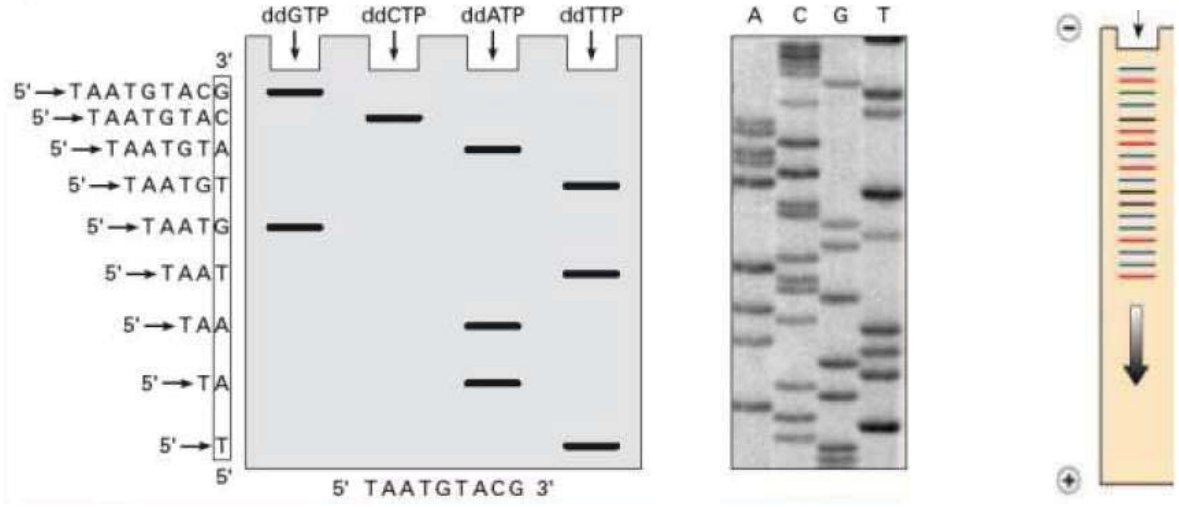
> A composition comprising four sets of oligonucleotides, wherein oligonucleotides of each of the four sets are distinguishably labeled with a different type of fluorophore from the oligonucleotides of the other three sets.

Promega argues that this claim is anticipated by the '800 patent. It points out that fluorescent Sanger sequencing, disclosed in the '800 patent, involves four separate reactions, and suggests that four distinguishable fluorophores, in four different colors, are needed to distinguish the results of the four reactions. That's not the case: as I explain below, the outputs of the four reactions could be kept separate and measured on four different gel tracks, in which event only a single color would be necessary. The '800 patent does not anticipate claim 67.

Obviousness. But it may render it obvious; and other prior art references, such as the Ruth '882 patent, might do this as well. Like claims 62 and 66, claim 67 requires fluorescently tagged oligonucleotides, but unlike those claims it does not require that the oligonucleotides be extendable. Many prior art references—such as the Ruth '882 patent, the application for which was filed in February 1983—explained how to attach fluorescent tags to oligonucleotides, even though it was uncertain whether the resulting oligonucleotides could always be extended. See Ruth report, Dec. 7, 2012 (dkt. 290-1), at 19–23; Dovichi deposition, May 6, 2013 (dkt. 390), at 267:16–19 ("there's a long and rich history…of people who employed fluorescently labeled oligonucleotides"). This could be done using fluorophores with many different spectra—colors distinct enough from each other to be distinguishable by a computer (Ruth '882 patent, 3:56-4:3). So a person of ordinary skill would have found it straightforward to tag four different sets of oligonucleotides with four distinguishable fluorophores.

The more difficult question is whether such a person would have been motivated to do this. The prior art need not contain an explicit "teaching, suggestion, or motivation

to combine known elements" for a claim to be obvious, but a person of skill must have had "an apparent reason to combine the known elements in the fashion claimed by the patent." *KSR International Co. v. Teleflex, Inc.*, *supra*, 550 U.S. at 418. The reason biochemists would mix four distinguishable sets of fluorophores in Sanger sequencing is to avoid having to run four separate reactions to measure the tagged DNA strands. Remember that Sanger sequencing requires creating and measuring DNA strands of different lengths ending in the same nucleotide base. The strands are measured using a process called "electrophoresis"—they are placed in a gel and separated by length with an electric current. The distance that each oligonucleotide travels across the gel indicates the length of the strand, revealing the position of the nucleotide base at the end of the strand. For example, by creating strands ending in the nucleotide thymine (T) and running those strands through electrophoresis, one can identify all thymine bases in the DNA sequence. This operation must be performed four separate times for each target strand—once for each possible nucleotide bases (A, C, G, and T)—to reveal the identity of each base in the DNA sequence. If radioactive tags, or fluorescent tags of a single color, are used, all of the bases give off the same signal, so scientists must keep the four bases separate by running the oligonucleotides on four different gel tracks. (A diagram of this process is shown at left below, and an actual example at center.) But if a different color is used for each base, the four bases emit different signals and a single track can be used (illustrated at right below), reducing time and expense.



Mixing four sets of fluorescent oligonucleotides is therefore useful in fluorescent Sanger sequencing. But even before Caltech researchers developed that process, fluorescent oligonucleotides were useful for other types of reactions. An oligonucleotide described in the Ruth '882 patent could bind to a strand of DNA with a complementary sequence and if tagged could thus indicate whether the complementary sequence appeared on a target strand of DNA. These DNA "probes" were valuable well before fluo-

rescent sequencing was developed; Dovichi notes, for example, that they were key to a common technique called "Southern blotting," published in 1975. Dovichi rebuttal report, Jan. 15, 2013 (dkt. 297), at ¶ 36. Electrophoresis could be used to analyze these oligonucleotides, but researchers would have liked to analyze multiple strands at once and so would have sought a single-gel advance in technology even before 1984.

Promega points to evidence that researchers were aware of the potential benefits of multicolor tags even for non-sequencing uses. A 1982 research abstract noted that "a lot of information can be obtained form [*sic*] one column by using multi-color labeling. Now we are developing an automated real time fluorescence detection gel electrophoresis system." Masao Tsuchiya, Yuzuru Hushimi, and Yasunori Kinishita, "Fluorescent Labelling of DNA and Real Time Fluorescence Detection Gel Electrophoresis," 22 *Biophysics* supp., No. 2-E-19 (Sep. 25, 1982); see also Ruth report at 26–28. The abstract described this as an important development, although it could not be used for fluorescent sequencing because no one had yet published such a sequencing method. A person of ordinary skill who read the abstract would have been motivated to use its multicolor technique when analyzing DNA probes, in order to increase the number of probes he could process on a single gel. Leroy Hood, an inventor of the '096 patent, explained at his deposition that a person of ordinary skill in the art would have wanted to use multiple fluorescent tags in 1984 for non-sequencing reactions: "If you had 100,000 fragments that you'd like to map, being able to multi-plex and have a quarter as many measurement reactions for them would be very attractive…. [With] four different fluorescent dyes[, you] could multiplex four clones at a time to do the mapping, labeling each of the fragments from the clones with a different colored dye. It's exactly like the sequencing reactions." Hood deposition, May 23, 2013 (dkt. 391), at 37:4–20. Life Tech offers nothing to contradict this evidence that a person of ordinary skill would have had "an apparent reason" to attach different tags to four groups of oligonucleotides and mix them.

What are called "secondary considerations" are relevant to obviousness. If for example the market and the research community ignored a prior art reference but reacted quickly to the disclosure of the patented invention, that would be evidence that the earlier reference had not rendered the invention obvious—that the patent had revealed important information. Dovichi, Life Tech's expert on secondary considerations of nonobviousness, wanted to be permitted to testify that the Smith 1986 paper, which announced the inventions claimed in the '096 patent, was widely praised by biochemists, suggesting that the paper reported a major advance. I refused to allow him to so testify, because his only evidence of "praise" was the number of citations to the paper, and he neither distinguished positive from negative citations nor compared the total number to the number of citations to papers acknowledged to have announced major advances. He also had not attempted to allocate citations among different claims or concepts in the '096 patent. Life Tech has not shown that the biochemists who cited the Smith paper

considered the concept of using four fluorophores in oligonucleotide analysis to be novel: they might instead have been responding to the description of fluorescent Sanger sequencing, which was contained in the '800 patent. I was not impressed that Dovichi considered the total number of citations to the Smith paper—983—too many for him to read. No doubt. But he could have read a random sample of them to determine both the percentage of positive citations and which concepts if any the authors of the citing papers considered novel in the Smith paper. Also his expert report offered no opinion specific to claim 67. Nor does Life Tech present any other such evidence.

With such meager evidence, secondary considerations fall out of the case, leaving uncontested the facts—specifically the disclosure of fluorescent tags in the Ruth '882 patent and multicolor analysis in the research abstract—that demonstrate that the invention was obvious, thus warranting summary judgment. *KSR Int'l Co. v. Teleflex, Inc.*, *supra*, 550 U.S. at 427; *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1366, 1370–73 (Fed. Cir. 2011).

Obviousness-type Double Patenting. Even if the '800 patent were not prior art and therefore did not anticipate or render obvious the asserted claims of the '096 patent, it might nonetheless invalidate those claims under the doctrine of obviousness-type double patenting. I asked the parties to brief this issue and now address it pursuant to Fed. R. Civ. P. 56(f)(2), which permits a judge, after giving notice and a reasonable time to respond, to grant summary judgment "on grounds not raised by a party." Life Tech's argument that Promega has waived the double-patenting argument is therefore unavailing.

A patent application is not anticipated or rendered obvious by a prior application by the same inventor. But this rule unless qualified would open a loophole allowing a patentee to obtain a patent term in excess of the statutory period (in our case, 17 years from issuance) by patenting overlapping claims. It's true that an inventor is entitled to "*a* patent" on an invention, 35 U.S.C. § 101 (emphasis added), and therefore may not file identical claims, *In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993), but the claims need not be identical to pose a problem. Suppose a medical researcher invents a pill for use in a specific medical treatment. The researcher receives a patent in 1992 claiming the pill, and another in 2001 claiming the use of the pill in the medical treatment for which the pill was invented. No one could use the pill without infringing both claims, and so if the second claim remained enforceable after the first claim had expired the researcher would have received a patent term of more than 17 years.

The doctrine of obviousness-type double patenting plugs the loophole. A court may not allow a later claim by the same inventor if the earlier one is "so alike that granting both exclusive rights would effectively extend the life of patent protection"—with "so alike" meaning that the earlier claim anticipates or renders obvious the later one. *Pericone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1373 (Fed. Cir. 2005); see also *Eli*

Lilly & Co. v. Barr Labs, Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). Because the doctrine is meant to prevent an inventor from extending the life of his patent by means of patents subject to different terms for different claims covering the same innovation, the doctrine turns on what is claimed in the earlier patent. Double-patenting cases thus ordinarily require the court to construe the claims of the first patent so that they can be compared to the claims of the later one. *Id*. at 968. But the claims of the '800 patent are straightforward; neither party has identified terms in that patent that require judicial construction. Claim 1 describes "the oligonucleotide compound having the formula: [chemical diagram], wherein B is selected from the group consisting of a nucleoside base and their derivatives." The other claims are similar.

A claim in a later patent escapes the double-patenting rule even if the innovation is disclosed in the specification of the earlier patent, provided that it's not disclosed in the claims. *In re Kaplan*, *supra*, 789 F.2d at 1580. Life Tech argues that because the sequencing method is not explicitly described in the '800 claims, the doctrine of double patenting does not apply. But the court may examine the specification and other evidence to determine whether an application of an earlier claim would have been obvious. *Eli Lilly & Co. v. Teva Patenteral Medicines, Inc.*, 689 F.3d 1368, 1379–80 (Fed. Cir. 2012); *Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1298 (Fed. Cir. 2012). So I can consider the '800 specification's description of Sanger sequencing reactions involving certain linker arms. I must determine whether those reactions were an obvious application of the '800 claims.

Claim 62 and dependent claims. Recall that claim 62 describes "a method of nucleic acid sequence analysis" that uses an oligonucleotide with various properties. This method claim differs in three ways from claim 1 of the '800 patent: it involves any linkage ("covalent coupling") that allows the oligonucleotide to be specifically hybridized and extended, while the '800 patent claims only certain linker arms with these properties; it requires that the oligonucleotide bind to a fluorophore (via the linkage); and it claims a method of nucleic acid sequence analysis in which the oligonucleotide is hybridized and extended. But these differences are obvious and so invalidate claim 62 under the double-patenting doctrine. The requirement of a "method of nucleic acid sequence analysis" is satisfied by the pre-existing knowledge of Sanger sequencing. Because of the heightened interest in fluorescent tags, a person of ordinary skill would as I have already explained have found it obvious to attach a fluorophore to the linker arm if the resulting oligonucleotide would be effective in Sanger sequencing. And the specification of the '800 patent makes clear that each linker arm claimed by that patent was effective in that respect: it could connect a fluorophore to an oligonucleotide in such a way that it could be extended and used in sequence analysis. It is true that some chemical linkages not claimed in the '800 patent are also effective in sequencing. But claim 62 covers a genus—methods of sequence analysis that involve certain chemical linkages—

and by making clear that at least one such linkage existed the '800 patent rendered that genus obvious. "A later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim." *Eli Lilly & Co. v. Barr Laboratories, Inc.*, *supra*, 251 F.3d at 971.

Life Tech objects that without the specification of the '800 patent, a person of ordinary skill would not have known that the claimed linker arms were effective in sequencing. But claim 62 covers the main intended use of the linker arms. Double patenting "encompasses any use for a compound that is disclosed in the specification of an earlier patent claiming the compound and is later claimed as a method of using that compound." *Sun Pharmaceutical Industries v. Eli Lilly & Co.*, 611 F.3d 1381, 1386 (Fed. Cir. 2010). Upholding claim 62 would deny the public the benefits of the main use of the '800 claims after the full term of the '800 patent had expired. "It would shock one's sense of justice if an inventor could receive a patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted." *Eli Lilly & Co. v. Teva Patenteral Medicines, Inc.*, *supra*, 689 F.3d at 1379 (quoting *In re Byck*, 48 F.2d 665, 666 (C.C.P.A. 1931)).

Ordinarily when one of an inventor's patents invalidates another because of obviousness-type double patenting the inventor can file a "terminal disclaimer," which preserves his right to enforce the second patent until the date the first patent expires. 35 U.S.C. § 253; *Perricone v. Medicis Pharmaceutical Corp.*, *supra*, 432 F.3d at 1375. But because the '800 patent expired in 2009 and the '096 patent was not reissued until 2012 and Life Tech can seek damages only for infringement after that date, it cannot use a terminal disclaimer to avoid the application of the double-patenting doctrine.

I conclude that claim 62 is made obvious by the claims of the '800 patent and is therefore invalid under the doctrine of obviousness-type double patenting. Life Tech does not identify any additional elements of the dependent claims that would not have been obvious to a person of skill in the art, and so those claims are invalid as well.

Claim 66. Claim 66 is a composition claim (unlike claim 62, a method claim). Like 62, claim 66 differs from the claims in the '800 patent in including any linker arm that allows an oligonucleotide to be specifically hybridized and extended, rather than only certain linker arms with this property. But as I have explained, by claiming a species of linker arms that are effective in sequencing the '800 renders obvious the genus of all linker arms with these properties. Claim 66 also requires that the oligonucleotide be covalently coupled to a fluorophore; that it hybridize to a complementary strand of DNA to form a duplex; and that it be part of the same mixture as a polymerase. All these are implications of using the oligonucleotide in Sanger sequencing.

Essentially claim 66 covers a mixture that contains a linker arm described in the '800 patent (or a similar linker arm), which is produced by using the linker arm in sequencing, as the specification of the '800 patent directs. By claiming a mixture necessarily produced by a given method, claim 66 restricts the public's access to the method just as claim 62, which covers the method itself, does; and the doctrine of double patenting is equally applicable in such a situation. Claim 66 is therefore obvious under the claims of the '800 patent and invalid under the doctrine of double patenting.

Written description and enablement.

Promega seeks summary judgment that claims 62 (and its dependent claims) and 66 flunk the written description and enablement requirements, 35 U.S.C. § 112, on two grounds. "Compliance with the written description requirement is a question of fact but is amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008); see also *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072-73 (Fed. Cir. 2005). "Enablement is a question of law based on underlying factual findings." *MagSil Corp. v. Hitachi Global Storage Technologies, Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). Summary judgment is appropriate if the undisputed factual evidence establishes that the patent specification fails to teach a person of ordinary skill how to make and use the claimed invention. *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012).

Method of nucleic acid sequence analysis. Promega argues that the specification shows that at the time of the patent application Life Tech did not possess, and therefore may not claim, a "method of nucleic acid sequence analysis" other than the Sanger method of DNA sequencing. Because I have construed claim 62 to reach other methods, such as multiplex STR analysis, that the inventors of the '096 patent did not invent and did not possess, Promega argues that this claim is invalid.

Claim 62, remember, describes:

> A method of nucleic acid sequence analysis, comprising extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product, wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA, and wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

My *Markman* order of April 4 held that as a matter of claim construction the preamble to this claim—"a method of nucleic acid sequence analysis"—does not limit the claim to DNA sequencing (determining the identity and order of each and every nucleotide in a DNA sequence). The claim reaches "any method of obtaining information

about a genetic sequence." But I did not address whether the claim, so construed, is adequately supported by the patent's specification.

The specification must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc), quoting *Vas–Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1562–63 (Fed. Cir. 1991). "The purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification…. It is part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from practicing an invention for a period of time." *Id.* at 1353–54 (quotation marks omitted). The inventor of one species may not claim the genus and thereby block the public from using other species, species that he has not discovered but that belong to the genus to which the species he has discovered belongs. See *id.* at 1349–50; *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004).

In *Chiron*, for example, a patent claimed "monoclonal antibodies" with certain properties. The specification in the earliest application for the patent showed that inventors knew how to make only one of the three types of monoclonal antibodies known to science (murine antibodies), and not the other two (chimeric and humanized antibodies). The district court construed the claim for monoclonal antibodies to reach all three types. The Federal Circuit upheld the construction, but held that the specification was inadequate to support a claim for the entire genus of monoclonal antibodies. Similarly, claim 62 of the '096 patent claims all methods of nucleic acid sequence analysis, but the patent specification describes only one such method (the Sanger method).

Life Tech points out that a patent's specification need not describe every possible use of the claimed invention. A patent covering a painkiller, for example, would not be invalid simply because it was later discovered to be effective against heart disease. Had the '096 patent claimed only a method of extending a fluorescently labeled oligonucleotide along a complementary strand of DNA, it would be no defense that Promega wanted to use that method to perform multiplex STR analysis instead of DNA sequencing. But Promega's multiplex STR analysis is not a new use of the Sanger method; it is a different *method*, having different goals (DNA fingerprinting, rather than DNA sequencing) and different elements, such as polymerase chain reaction (PCR), which hadn't been invented in 1984 when the application for the '096 patent was first filed.

Claim 62 and its dependent claims are therefore invalid.

Specifically hybridized oligonucleotides. Promega argues also (but unavailingly, as I am about to show) that claims 62 and 66 are invalid because they claim a broader range of oligonucleotides than the specification enables. In order to enable, the patent's specification must provide enough detail so that one skilled in the art at the time of the applica-

tion could "make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *MagSil Corp. v. Hitachi Global Storage Technologies, Inc.*, *supra,* 687 F.3d at 1380–81.

Claims 62 and 66 each require an oligonucleotide to be specifically hybridized to a complementary strand of DNA. Promega points out that making a specifically hybridized oligonucleotide requires knowing the sequence of nucleotide bases in the complementary strand to which it will bind. In DNA sequencing applications the sequence of the target strand is unknown, so it is impossible to create an oligonucleotide specifically hybridized to the target strand. Instead, a known strand (called, as noted earlier, a cloning vector) is attached to the start of the target strand, and an oligonucleotide designed to bind to the cloning vector is attached to start the process of replicating the target strand. The '096 specification discloses the use of an oligonucleotide specifically hybridized to a cloning vector known as M13.

Some more recent methods of analyzing a strand's nucleic acid sequence—including multiplex STR analysis—use an oligonucleotide designed to bind directly to a known portion of the target strand. But when the '096 patent application was first filed the Human Genome Project was not yet underway, and so it would have been impossible to create an oligonucleotide designed to bind to most locations on the human genome, including the locations to which Promega's oligonucleotides bind in multiplex STR analysis. Therefore, says Promega, the inventors did not enable "the full scope of the claimed invention." *Magsil Corp. v. Hitachi Global Storage Technologies, Inc.*, *supra*, 687 F.3d at 1380.

Life Tech's expert Dr. Norman Dovichi counters that designing an oligonucleotide to bind to a *known* DNA sequence would have been relatively easy in 1984 and could have been accomplished by one skilled in the art without undue experimentation. Promega's summary judgment motion offers no expert testimony contradicting this conclusion. The invention is thus enabled for all known DNA sequences. That is enough. "The law does not expect an applicant to disclose knowledge invented or developed after the filing date." *Chiron Corp. v. Genentech, Inc.*, *supra*, 363 F.3d at 1254. As the Human Genome Project sequenced new regions of human DNA, one skilled in the art could design oligonucleotides to bind to those regions without undue experimentation, thus enabling new uses of the claimed invention. But the inventors of the '096 patent were not required to identify in advance all of the DNA sequences that their claimed oligonucleotides could bind to.

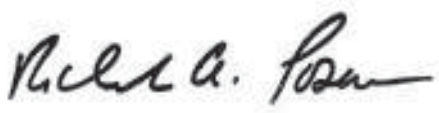
Promega argues that the written description requirement could not be satisfied unless the '096 specification recited the nucleotide sequence of every oligonucleotide within the scope of claims 62 and 66. The cases it cites, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323

F.3d 956 (Fed. Cir. 2002), do not require this. Both cases involved claims to specific genes or DNA sequences—genes encoding insulin in *Eli Lilly*, and nucleic acid probes with sequences found in specific bacteria in *Enzo*. The '096 patent claims, in contrast, involve oligonucleotides that can be designed to bind to a wide variety of known DNA sequences. The '096 patent's specification describes one working example (the oligonucleotide specifically hybridized to the M13 cloning vector). It would be impractical to require more, and unnecessary because, as Dr. Dovichi explains, designing oligonucleotides to hybridize to additional locations would not require undue experimentation (if it did, this would imply that the disclosures in the patent itself were insufficient to enable a reader to create the patented invention) once the sequence of the target location was known.

In sum, the '096 patent's specifications adequately describe and enable the specifically hybridized oligonucleotides recited by claims 62 and 66.

Conclusion

All the claims of the '096 patent asserted by Life Tech are invalid, whether Smith '800 is considered prior art or not. Claim 62 and its dependent claims are invalid because failing to meet the written description requirement, because anticipated by the '800 patent and as double patenting. Claim 66 fails because anticipated by the '800 patent and as double-patenting. And claim 67 is invalid as obvious in light of the Ruth '882 patent and the reference in the research abstract that I mentioned.



United States Circuit Judge

June 12, 2013

TAB 6

AO 450 (Rev. 11/11) Judgment in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of Illinois

Promega Corp.	)	
Plaintiff	)	
v.	)	Civil Action No. 1:13-cv-02333
Applied Biosystems, LLC, et al.	)	
Defendant	)	

JUDGMENT IN A CIVIL ACTION

The court has ordered that *(check one)*:

☐ the plaintiff *(name)* _____ recover from the defendant *(name)* _____ the amount of _____ dollars ($ _____), which includes prejudgment interest at the rate of _____ %, plus post judgment interest at the rate of _____ % per annum, along with costs.

☐ the plaintiff recover nothing, the action be dismissed on the merits, and the defendant *(name)* _____ _____ recover costs from the plaintiff *(name)* _____ _____ .

☑ other: For the reasons set forth in the accompanying Opinion, Promega's "motion for summary judgment that the asserted claims of the '096 patent are invalid" is granted. Judgment is ordered entered in favor of Promega on its claim for declaratory judgment of invalidity of U.S. Patent No. RE43,096. All remaining motions and all other pending claims and counterclaims are dismissed as moot.

This action was *(check one)*:

☐ tried by a jury with Judge _____ presiding, and the jury has rendered a verdict.

☐ tried by Judge _____ without a jury and the above decision was reached.

☑ decided by Judge Richard A. Posner on a motion for summary judgment of invalidity of all asserted claims of U.S. Patent No. RE43,096.

Date: June 13, 2013

CLERK OF COURT

Mark Fratti

Signature of Clerk or Deputy Clerk

TAB 7

US00RE43096E

(19) **United States**

(12) **Reissued Patent**
Smith et al.

(10) **Patent Number: US RE43,096 E**

(45) **Date of Reissued Patent: Jan. 10, 2012**

(54) **TAGGED EXTENDABLE PRIMERS AND EXTENSION PRODUCTS**

(75) Inventors: **Lloyd M. Smith**, Madison, WI (US); **Leroy E. Hood**, Seattle, WA (US); **Michael W. Hunkapiller**, San Carlos, CA (US); **Timothy Hunkapiller**, Mercer Island, WA (US); **Charles R. Connell**, Redwood City, CA (US)

(73) Assignee: **California Institute of Technology**, Pasadena, CA (US)

(21) Appl. No.: **10/389,663**

(22) Filed: **Mar. 13, 2003**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **6,200,748**
Issued: **Mar. 13, 2001**
Appl. No.: **08/484,340**
Filed: **Jun. 7, 1995**

U.S. Applications:

(63) Continuation of application No. 08/361,176, filed on Dec. 21, 1994, now Pat. No. 5,821,058, which is a continuation of application No. 07/898,019, filed on Jun. 12, 1992, now abandoned, which is a continuation of application No. 07/660,160, filed on Feb. 21, 1991, now abandoned, which is a continuation of application No. 07/106,232, filed on Oct. 7, 1987, now abandoned, which is a continuation-in-part of application No. 06/722,742, filed on Apr. 11, 1985, now abandoned, which is a continuation-in-part of application No. 06/689,013, filed on Jan. 2, 1985, now abandoned, which is a continuation-in-part of application No. 06/570,973, filed on Jan. 16, 1984, now abandoned.

(51) **Int. Cl.**
C12Q 1/68 (2006.01)
G01N 27/447 (2006.01)

(52) **U.S. Cl.** **435/6.1**; 536/24.3; 536/25.32; 536/26.6; 435/91.2; 435/91.1; 435/91.51

(58) **Field of Classification Search** 435/6, 91.2; 536/24.33, 23.1, 24.3, 26.6
See application file for complete search history.

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Primary Examiner — Stephanie K Mummert

(74) *Attorney, Agent, or Firm* — James S. Keddie; Carol L. Francis; Bozicevic, Field & Francis, LLP

(57) **ABSTRACT**

This invention provides a duplex comprising an oligonucleotide primer and a template, wherein the primer is coupled chemically to a chromophore or fluorophore so as to allow chain extension by a polymerase. In one embodiment, the primer is extended by a polymerase to generate the complement of the template. In a further embodiment, the extended primer is separated from the template for use in a number of methods, including sequencing reactions. Methods of generating these compositions of matter are further provided.

97 Claims, 6 Drawing Sheets

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Kagakukai ed., "Fluorescence tagging" "*Biochemistry Experiments Course 2, Nucleic Acid Chemistry III*" (1977) pp. 299-317.
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Tsuchiya, M. (1982). "Development of DNA Fluorescent Labeling and Real-Time Fluorescence Detection Gel Electrophoresis Mehtods," *Biophysics* 22:S170 (English translation attached).

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5'...ATGCTCTGCAGGAATAC...3'
3'...TACGAGACGTCCTTATG...5'
PST I
5'...ATGCTCTGCA 3'
3'...TACGAG 5'
+
3'ACGTNNT—FITC 5'
T4 DNA
5'...ATGCTCTGCA 3'
3'...TACGAGACGTNNT—FITC

FIG. 1A

FIG. 1B

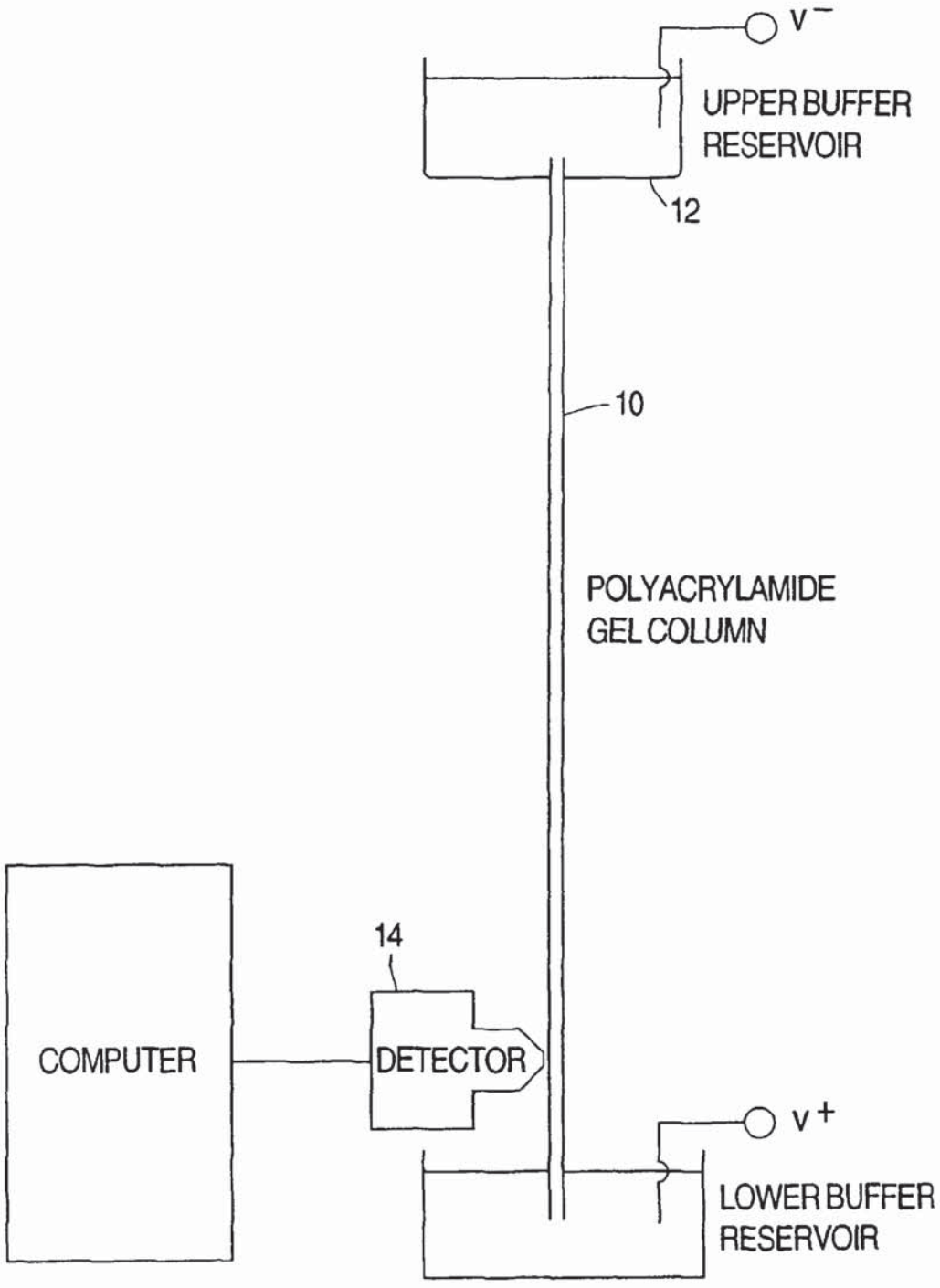
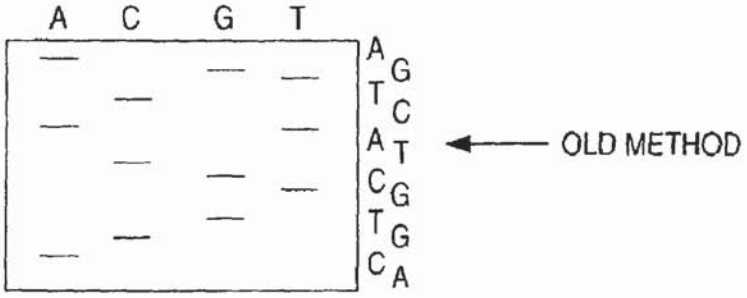

V −
UPPER BUFFER RESERVOIR
12
10
POLYACRYLAMIDE GEL COLUMN
14
COMPUTER
DETECTOR
V +
LOWER BUFFER RESERVOIR

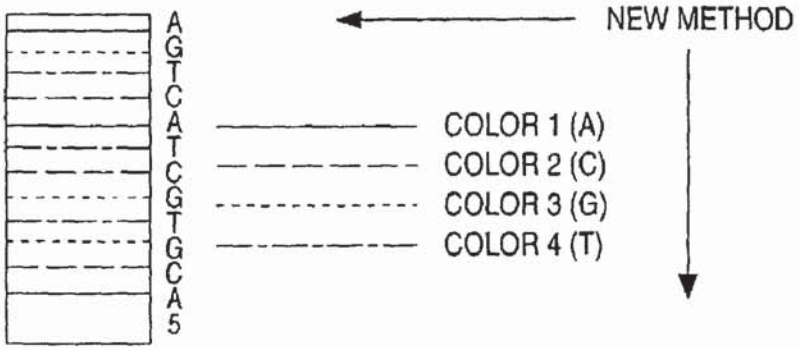
FIG. 2

I) A HYPOTHETICAL DNA SEQUENCE
5' ACGTGCTACTGA 3'

II) IDEALIZED AUTORADIOGRAM OF POLYACRYLAMIDE SLAB GEL PRODUCED IN CHAIN TERMINATION SEQUENCING ACCORDING TO THE PRIOR ART



III) IDEALIZED DIAGRAM OF COLORED DNA BANDS ON TUBE ACRYLAMIDE GEL, PRODUCED ACCORDING TO PRESENT INVENTION



IV) IDEALIZED OUTPUT FROM DETECTION OF COLORED BANDS ON ABOVE TUBE GEL

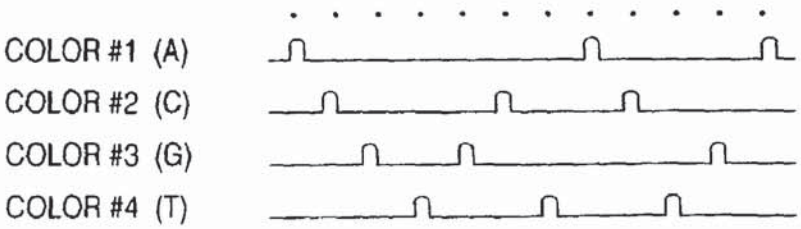


FIG. 3

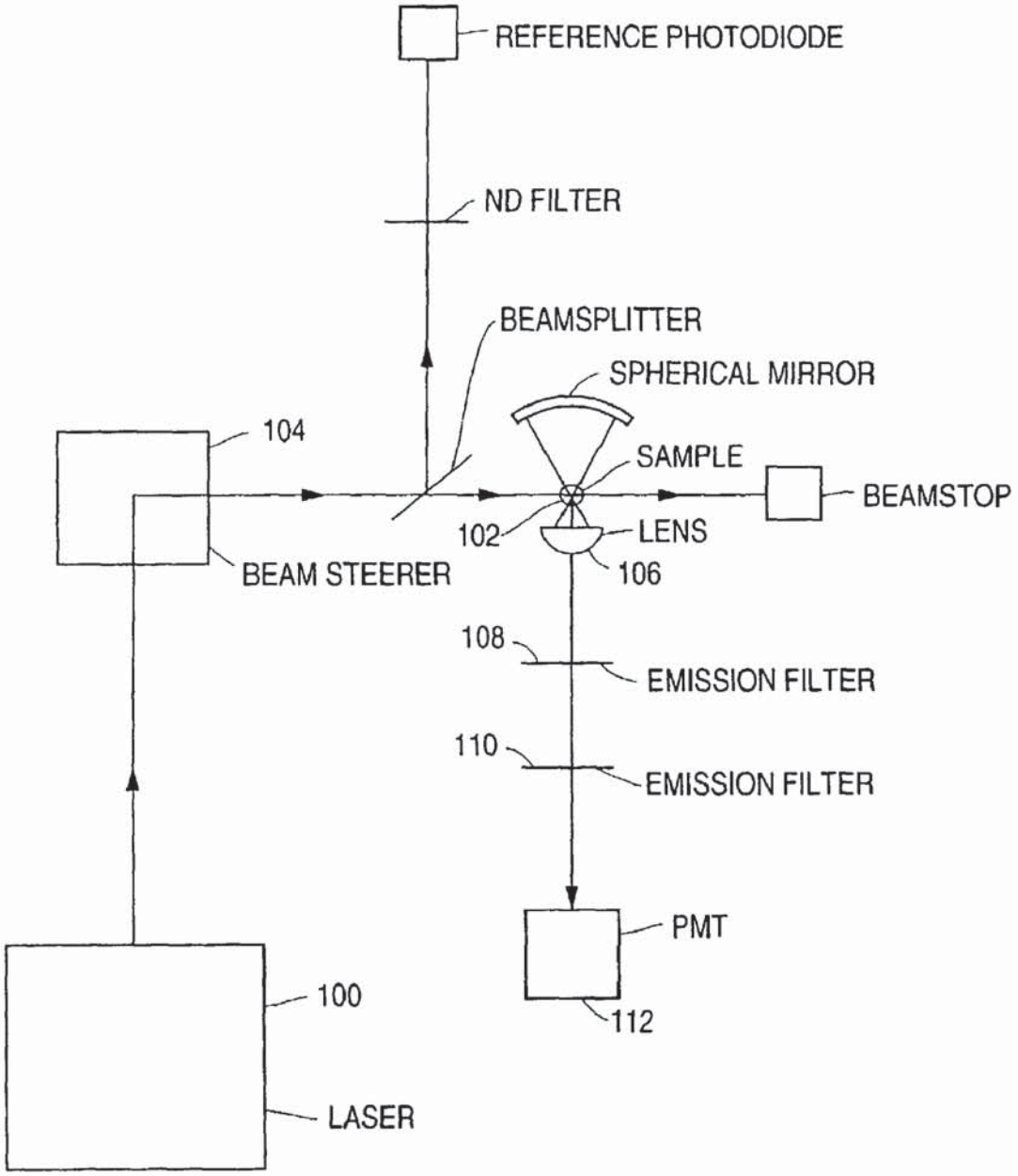

REFERENCE PHOTODIODE
ND FILTER
BEAMSPLITTER
SPHERICAL MIRROR
104
SAMPLE
BEAMSTOP
102
LENS
BEAM STEERER
106
108
EMISSION FILTER
110
EMISSION FILTER
PMT
100
112
LASER

FIG. 4

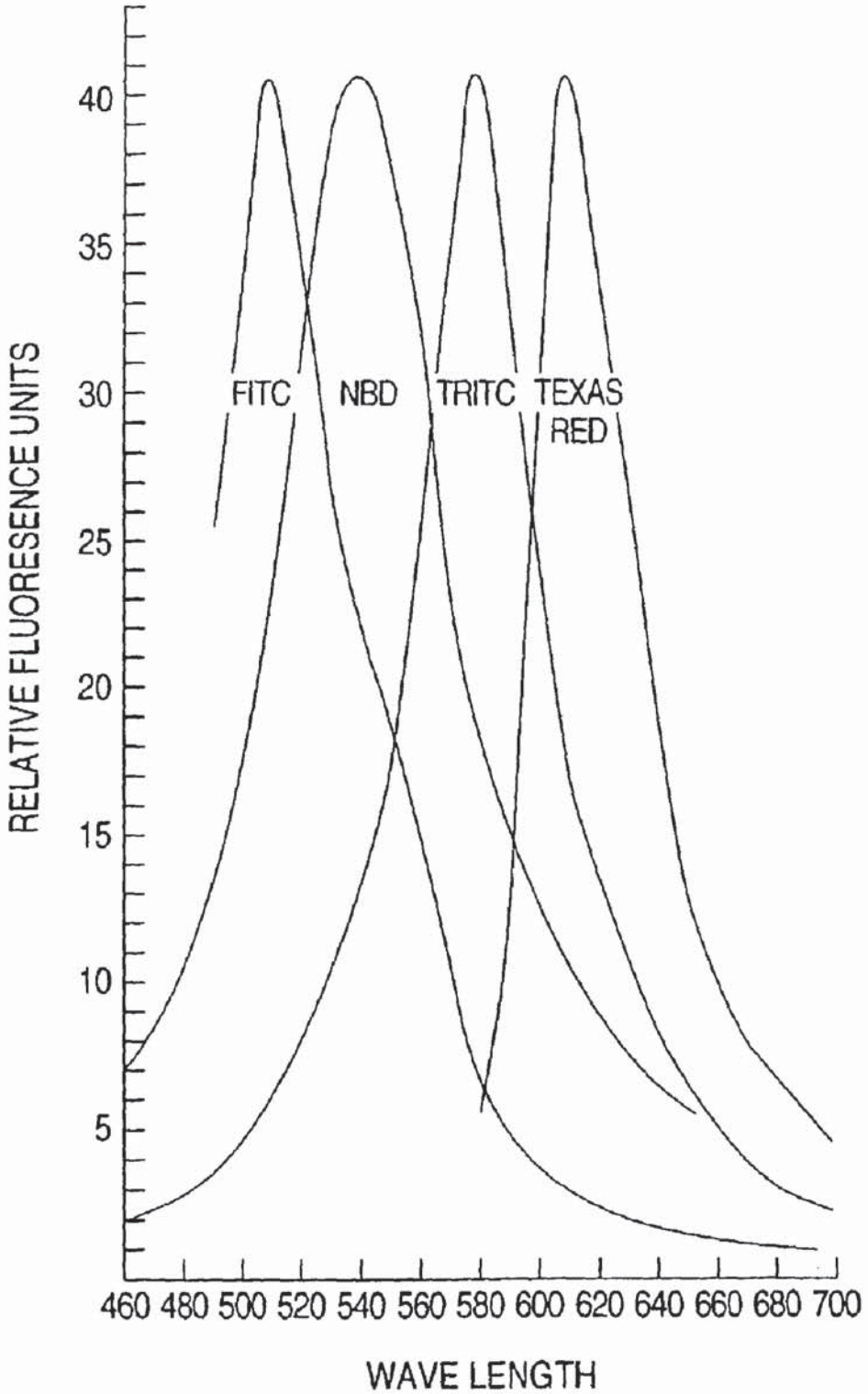

RELATIVE FLUORESENCE UNITS
40
35
30
25
20
15
10
5
FITC
NBD
TRITC
TEXAS RED
460 480 500 520 540 560 580 600 620 640 660 680 700
WAVE LENGTH

FIG. 5

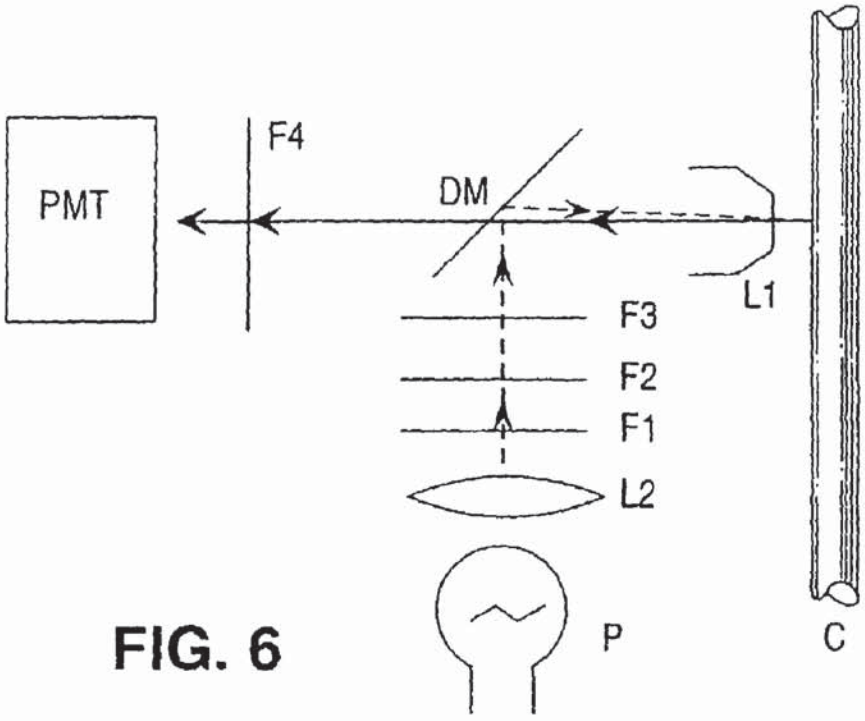

PMT
F4
DM
L1
F3
F2
F1
L2
P
C

FIG. 6

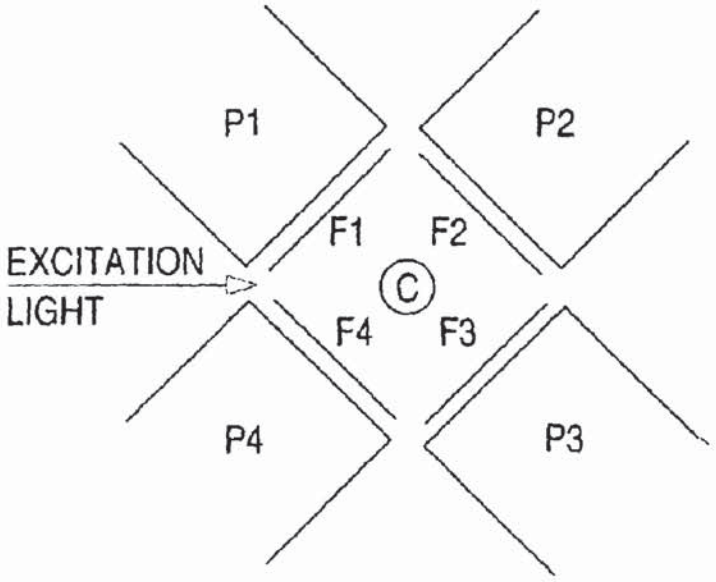

P1
P2
F1
F2
EXCITATION
LIGHT
C
F4
F3
P4
P3

FIG. 7

TAGGED EXTENDABLE PRIMERS AND EXTENSION PRODUCTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application is a continuation of application Ser. No. 08/361,176 filed Dec. 21, 1994, now U.S. Pat. No. 5,821,058 which is a continuation of application Ser. No. 07/898,019, filed Jun. 12, 1992, now abandoned, which is a continuation of application Ser. No. 07/660,160, filed Feb. 21, 1991, now abandoned, which is a continuation of application Ser. No. 07/106,232, filed Oct. 7, 1987, now abandoned, which is a CIP of application Ser. No. 06/722,742, filed Apr. 11, 1985, now abandoned, which is CIP of application Ser. No. 06/689,013,filed Jan. 2, 1985, now abandoned, which is a CIP of application Ser. No. 06/570,973, filed Jan. 16, 1984, now abandoned.

BACKGROUND OF THE INVENTION

The development of reliable methods for sequence analysis of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) has been one of the keys to the success of recombinant DNA and genetic engineering. When used with the other techniques of modern molecular biology, nucleic acid sequencing allows dissection and analysis of animal, plant and viral genomes into discrete genes with defined chemical structure. Since the function of a biological molecule is determined by its structure, defining the structure of a gene is crucial to the eventual manipulation of this basic unit of hereditary information in useful ways. Once genes can be isolated and characterized, they can be modified to produce desired changes in their structure that allow the production of gene products—proteins—with different properties than those possessed by the original proteins. Microorganisms into which the natural or synthetic genes are placed can be used as chemical "factories" to produce large amounts of scarce human proteins such as interferon, growth hormone, and insulin. Plants can be given the genetic information to allow them to survive harsh environmental conditions or produce their own fertilizer.

The development of modem nucleic acid sequencing methods involved parallel developments in a variety of techniques. One was the emergence of simple and reliable methods for cloning small to medium-sized strands of DNA into bacterial plasmids, bacteriophages, and small animal viruses. This allowed the production of pure DNA in sufficient quantities to allow its chemical analysis. Another was the near perfection of gel electrophoretic methods for high resolution separation of oligonucleotides on the basis of their size. The key conceptual development, however, was the introduction of methods of generating size-nested sets of fragments cloned, purified DNA that contain, in their collection of lengths, the information necessary to define the sequence of the nucleotides comprising the parent DNA molecules.

Two DNA sequencing methods are in widespread use. These are the method of Sanger, F., Nicken, S. and Coulson, A. R. Proc. Natl. Acad. Sci. U.S.A. 74, 5463 (1977) and the method of Maxam, A. M. and Gilbert, W. Methods in Enzymology 65, 499-599 (1980).

The method developed by Sanger is referred to as the dideoxy chain termination method. In the most commonly used variation of this method, a DNA segment is cloned into a single-stranded DNA phage such as M13. These phage DNAs can serve as templates for the primed synthesis of the complementary strand by the Klenow fragment of DNA polymerase I. The primer is either a synthetic oligonucleotide or a restriction fragment isolated from the parental recombinant DNA that hybridizes specifically to a region of the M13 vector near the 3" end of the cloned insert. In each of four sequencing reactions, the primed synthesis is carried out in the presence of enough of the dideoxy analog of one of the four possible deoxynucleotides so that the growing chains are randomly terminated by the incorporation of these "dead-end" nucleotides. The relative concentration of dideoxy to deoxy forms is adjusted to give a spread of termination events corresponding to all the possible chain lengths that can be resolved by gel electrophoresis. The products from each of the four primed synthesis reactions are then separated on individuals tracks of polyacrylamide gels by the electrophoresis. Radioactive tags incorporated in the growing chains are used to develop an autoradiogram image of the pattern of the DNA in each electrophoresis track. The sequence of the deoxynucleotides in the cloned DNA is determined from an examination of the pattern of bands in the four lanes.

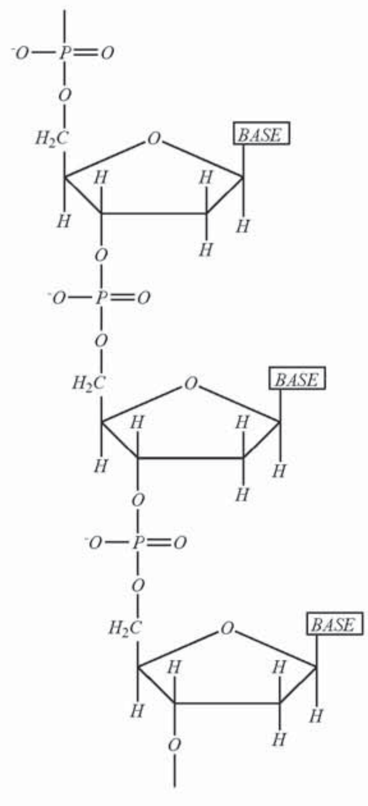
The method developed by Maxam and Gilbert uses chemical treatment of purified DNA to generate size-nested sets of DNA fragments analogous to those produced by the Sanger method. Single or double-stranded DNA, labeled with radioactive phosphate at either the 3' or 5' end, can be sequenced by this procedure. In four sets of reactions, cleavage is induced at one or two of the four nucleotide bases by chemical treatment. Cleavage involves a three-stage process: modification of the base, removal of the modified base from its sugar, and strand scission at that sugar. Reaction conditions are adjusted so that the majority of end-labeled fragments generated are in the size range (typically 1 to 400 nucleotides) that can be resolved by gel electrophoresis. The electrophoresis, autoradiography, and pattern analysis are carried out essentially as is done for the Sanger method. (Although the chemical fragmentation necessarily generates two pieces of DNA each time it occurs, only the piece containing the end label is detected on the autoradiogram.)

Both of these DNA sequencing methods are in widespread use, and each has several variations.

For each, the length of sequence that can be obtained from a single set of reactions is limited primarily by the resolution of the polyacrylamide gels used for electrophoresis. Typically, 200 to 400 bases can be read from a single set of gel tracks. Although successful, both methods have serious drawbacks, problems associated primarily with the electrophoresis procedure. One problem is the requirement of the use of radiolabel as a tag for the location of the DNA bands in the gels. One has to contend with the short half-life of phosphorus-32, and hence the instability of the radiolabeling reagents, and with the problems of radioactive disposal and handling. More importantly, the nature of autoradiography (the film image of a radioactive gel band is broader than the band itself) and the comparison of band positions between four different gel tracks (which may or may not behave uniformly in terms of band mobilities) can limit the observed resolution of bands and hence the length of sequence that can be read from the gels. In addition, the track-to-track irregularities make automated scanning of the autoradiograms difficult—the human eye can presently compensate for these irregularities much better than computers can. This need for manual "reading" of the autoradiograms is time-consuming, tedious and error-prone. Moreover, one cannot read the gel patterns while the electrophoresis is actually being performed, so as to be able to

terminate the electrophoresis once resolution becomes insufficient to separate adjoining bands, but must terminate the electrophoresis at some standardized time and wait for the autoradiogram to be developed before the sequence reading can begin.

An oligonucleotide is a short polymer consisting of a linear sequence of four nucleotides in a defined order. The nucleotide subunits are joined by phosphodiester linkages joining the 3' hydroxyl moiety of one nucleotide to the 5' hydroxyl moiety of the next nucleotide. An example of an oligonucleotide is 5' ApCpGpTpApTpGpGpCp 3'. The letters A, C, G and T refer to the nature of the purine of pyrimidine base coupled at the 1-position of deoxyribose. A, adenine; C, cytosine; G, guanine; T, thymidine. P represents the phosphodiester bond. The structure of a section of an oligonucleotide is shown below.



The single stranded oligonucleotides of this invention are further characterized by being homogenous with respect to the sequence of the nucleoside subunits and are of uniform molecular weight.

Synthetic oligonucleotides are powerful tools in modern molecular biology and recombinant DNA work. There are numerous applications for these molecules, including a) as probes for the isolation of specific genes based on the protein sequence of the gene product, b) to direct the in vitro mutagenesis of a desired gene, c) as primers for DNA synthesis on a single-stranded template, d) as steps in the total synthesis of genes, and many more, reviewed in Wm. R. Bahl et al, Prog. Nucl. Acid Res. Mol. Biol., 21, 101 (1978).

A very considerable amount of effort has therefore been devoted to the development of efficient chemical methods for the synthesis of such oligonucleotides. A brief review of these methods as they have developed to the present is found in Crockett, G. C., Aldrichimica Acta 16(3), 47–55 (1983). The best methodology currently available utilizes the phosphoramidite derivatives of the nucleosides in combination with a solid phase synthetic procedure, Matteucci et al, J. Am. Chem. Soc., 103, 3185 (1981); and Beaucage et al, M. H. Tet. Lett., 22 (20), 1858-1862 (1981). Oligonucleotides of length up to 30 bases may be made on a routine basis in this matter, and molecules as long as 50 bases have been made. Machines that employ this technology are now commercially available.

There are other reports in the literature of the derivitization of DNA. A modified nucleoside triphosphate has been developed wherein a biotin group is conjugated to an aliphatic amino group at the 5 position of uracil, Langer et al, Proc. Nat. Acad. Sci., U.S.A., 78, 6633-6637 (1981). This nucleotide derivative is effectively incorporate into double stranded DNA. Once in DNA it may be bound by anti-biotin antibody which can then be used for detection by fluorescence or enzymatic methods. The DNA which has had biotin conjugated nucleosides incorporated therein by the method of Langer et al is fragmented into smaller single and double stranded pieces which are heterogeneous with respect to the sequence of nucleoside subunits and variable in molecular weight. Draper and Gold, Biochemistry, 19, 1774-1781 (1980), reported the introduction of aliphatic amino groups by a bisulfite catalyzed transamination reaction, and their subsequent reaction with the fluorescent tag. In Draper and Gold the amino group is attached directly to the pyrimidine base. The amino group so positioned inhibits hydrogen bonding and for this reason, these materials are not useful in hybridization and the like. Chu et al, Nucleic Acid Res. 11(18), 6513-6529 (1983), have reported a method for attaching an amine to the terminal 5' phosphate of oligonucleotides or nucleic acids.

There are many reasons to want a method for covalently attaching other chemical species to synthetic oligonucleotides. Fluorescent dyes attached to the oligonucleotides permits one to eliminate radioisotopes from the research, diagnostic and clinical procedures in which they are used, and improve shelf-life availability. As described in the assignee's co-pending application for a DNA sequencing machine (Serial No. the synthesis of fluorescent-labeled oligonucleotides permits the automation of the DNA sequencing process.

The invention of the present patent application addresses these and other problems associated with DNA sequencing procedures and is believed to represent a significant advance in the art. The preferred embodiment of the present invention represents a further and distinct improvement.

SUMMARY OF THE INVENTION

Briefly, this invention comprises a novel process for the electrophoetic analysis of DNA fragments produced in DNA sequencing operations wherein chromophores or fluorophores are used to tag the DNA fragments produced by the sequencing chemistry and permit the detection and characterization of the fragments as they are resolved by electrophoresis through a gel. The detection employs an absorption or fluorescent photometer capable of monitoring the tagged bands as they are moving through the gel.

This invention further comprises a novel process for the electrophoretic analysis of DNA fragments produced in DNA sequencing operations wherein a set of four chromophores are used to tag the DNA fragments produced by the sequencing chemistry and permit the detection and characterization of the fragments as they are resolved by electrophoresis through a gel; the improvement wherein the four different fragment sets are tagged with the fluorophores fluorescein, Texas Red, tetramethyl rhodamine, and 7-nitrobenzofurazan.

This invention also includes a novel system for the electrophoretic analysis of DNA fragments produced in DNA sequencing operations comprising:

a source of chromophore or fluorescent tagged DNA fragments.

a zone for containing an electrophoresis gel,

means for introducing said tagged DNA fragments to said zone; and

photometric means for monitoring or detecting said tagged DNA fragments as they move through and are separated by said gel.

It is an object of this invention to provide a novel process for the sequence analysis of DNA.

It is another object of our invention to provide a novel system for the analysis of DNA fragments.

More particularly, it is an object of this invention to provide an improved process for the sequence analysis of DNA.

These and other objects and advantages of this invention will be apparent from the detailed description which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Turning to the drawings:

FIG. **1** is an illustration of one means of end-labeling a DNA fragment with a fluorescent tag. Pst. I and T4 DNA ligase are enzymes commonly used in recombinant DNA research.

FIG. **2** is a block diagram of automated DNA sequencer, gel electrophoretic system.

FIG. **3** is a comparison of the type of data produced by DNA sequencing of the sequence shown in FIG. **1**.

FIG. **4** is a block diagram of a preferred DNA sequencer according to this invention.

FIG. **5** shows the emission spectra for the four fluorophores used as tags in the preferred embodiment of this invention.

FIG. **6** is a schematic diagram of a possible optical configuration in the detector unit. P, lamp source; L**1**, objective lens; L**2**, collimating lens; F**1**, UV blocking filter; F**2**, heat blocking filter; F**3**, band pass excitation filter; F**4**, long pass emission filter; DM, dichroic mirror; C, polyacrylamide gel; PMT, photomultiplier tube.

FIG. **7** is a schematic diagram of another possible optical configuration in the detector unit. F**1** to F**4** are bandpass filters centered at the emission maximum of the different dyes. P**1** to P**4** are photomultiplier tubes. The excitation light is of a wavelength such that it is not transmitted through any of the filters F**1** to F**4**.

DETAILED DESCRIPTION OF THE INVENTION

In the previous methods of DNA sequencing, including those based on the Sanger dideoxy chain termination method, a single radioactive label, phosphorus-32, is used to identify all bands on the gels. This necessitates that the fragment sets produced in the four synthesis reactions be run on separate gel tracks and leads to the problems associated with comparing band mobilities in the different tracks. This problem is overcome in the present invention by the use of a set of four chromophores or fluorophores with different absorption or fluorescent maxima, respectively. Each of these tags is coupled chemically to the primer used to initiate the synthesis of the fragment strands. In turn, each tagged primer is then paired with one of the dideoxynucleotides and used in the primed synthesis reaction with the Klenow fragment of DNA polymerase.

The primers must have the following characteristics. 1) They must have a free 3' hydroxyl group to allow chain extension by the polymerase. 2) They must be complementary to a unique region 3' of the cloned insert. 3) They must be sufficiently long to hybridize to form a unique, stable duplex. 4) The chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase.

Conditions 1, 2 and 3 above are satisfied by several synthetic oligonucleotide primers which are in general use for Sanger-type sequencing utilizing M13 vectors.

One such primer is the 15 mer 5' CCC AG TCA CGA CGT T 3' where A, C, G and T represent the four different nucleoside components of DNA; A, adenosine; C, cytosine; G, guanosine; T, thymidine.

In the preferred embodiment of the present invention a set of four fluorophores with different emission spectra, respectively, are used. These different emission spectra are shown in FIG. **5**. Each of these tags is coupled chemically to the primer used to initiate the synthesis of the fragment strands. In turn, each tagged primer is then paired with one of the dideoxynucleotides and used in the primed synthesis reaction with the Klenow fragment of DNA polymerase.

The dyes used must have high extinction coefficients and/or reasonably high quantum yields for fluorescence. They must have well resolved adsorption maxima and/or emission masima. Representative of such amino reactive dues are: fluorescein isothiocyanage (FITC, $\lambda_{max}^{Ex}=495$, $\lambda_{max}^{Em}=520$, $\epsilon_{495}\cong 8\times10^4$), tetramethyl rhodamine isothiocyanate (TMRITC, $\lambda_{max}^{Ex}=550$, $\lambda_{max}^{Em}=578$, $\epsilon_{550}\cong 4\times10^4$), and substituted rhodamine isothiocyanate (XRITC, $\lambda=580$, $\lambda_{max}^{Em}=604$, $\epsilon_{580}\cong 8\times10^4$)

where λ represents the wavelength in nanometers, Ex is excitation, Em is emission, max is maximum, and ϵ is the molar extinction coefficient. These dyes have been attached to the M13 primer and the conjugates electrophoresed on a 20% polyacrylamide gel. The labeled,primers are visible by both their absorption and their fluorescence in the gel. All four labeled primers have identical electrophoretic mobilities. The dye conjugated primers retain their ability to specifically hybridize to DNA, as demonstrated by their ability to replace the underivitized oligonucleotide normally used in the sequencing reactions.

The chemistry for the coupling of the chromophoric or fluorophoric tags is described in assignee's copending patent applications Ser. No. 565,010, filed Dec. 20, 1983, now abandoned, and Ser. No. 709,579, filed Mar. 8, 1985, the disclosures of which are expressly incorporated herein by reference. The strategy used is to introduce an aliphatic amino group at the 5' terminus as the last addition in the synthesis of the oligonucleotide primer. This reactive amino group may then readily be coupled with a wide variety of amino reactive fluorophores or chromophores. This approach aids compatibility of the labeled primers with condition 4 above.

End Labeling of DNA for Use With Maxam/Gilbert Method. In the Maxam/Gilbert method of DNA sequencing, the end of the piece of DNA whose sequence is to be determined must be labeled. This is conventionally done enzymatically using radioactive nucleosides. In order to use the Maxam/Gilbert method in conjunction with the dye detection scheme described in this invention, the DNA piece must be labeled with dyes. One manner in which this maybe accomplished is shown in FIG. **1**. Certain restriction endonucleases generate what is known as a 3' overhang as the product of DNA cleavage. These enzymes generate a "sticky end," a short stretch of single stranded DNA at the end of a piece of double stranded DNA. This region will anneal with a complementary stretch of DNA, which may be covalently joined to the duplex DNA with the enzyme ligase. In this manner one of

the strands is covalently linked to a detectable moiety. This moiety may be a dye, an amino group or a protected amino group (which could be deprotected and reacted with dye subsequent to the chemical reactions).

Sequencing Reactions. The dideoxy sequencing reactions are performed in the standard fashion Smith, A. J. H., Methods in Enzymology 65, 560–580 (1980), except that the scale may be increased if necessary to provide an adequate signal intensity in each band for detection. The reactions are done using a different color primer for each different reaction. No radiolabeled nucleoside triphosphate need be included in the sequencing reaction.

The Maxam/Gilbert sequencing reactions are performed in the usual manner, Gil, S. F. Aldrichimica Acta 16(3), 59–61 (1983), except that the end label is either one or four colored dyes, or a free or protected amino group which may be reacted with dye subsequently.

Detection. There are many different ways in which the tagged molecules which have been separated by length using polyacrylamide gel electrophoresis may be detected. Four illustrative modes are described below. These are i) detection of the fluorescence excited by light of different wavelengths for the different dyes, ii) detection of fluorescence excited by light of the same wavelength for the different dyes, iii) elution of the molecules from the gel and detection by chemiluminescence, and iv) detection by the absorption of light by molecules. In modes i) and ii) the fluorescence detector should fulfill the following requirements. a) The excitation light beam should not have a height substantially greater than the height of a band. This is normally in the range of 0.1 to 0.5 mm. The use of such a narrow excitation beam allows the attainment of maximum resolution of bands. b) The excitation wavelength can be varied to match the absorption maxima of each of the different dyes or can be a single narrow, high intensity light band that excites all four fluorophores and does not overlap with any of the fluorescence emission. c) The optical configuration should minimize the flux of scattered and reflected excitation light to the photodetector **14**. The optical filters to block out scattered and reflected excitation light are varied as the excitation wavelength is varied. d) The photodetector **14** should have a fairly low noise level and a good spectral response and quantum efficiency throughout the range of the emission of the dyes (500 to 600 nm for the dyes listed above). e) The optical system for collection of the emitted fluorescence should have a high numerical aperture. This maximizes the fluorescence signal. Furthermore, the depth of field of the collection optics should include the entire width of the column matrix.

Two illustrative fluorescence detection systems are diagrammed in FIGS. **6** and **7**. The system in FIG. **6** is compatible with either single wavelength excitation or multi wavelength excitation. For single wavelength excitation, the filter F**4** is one of four band pass filters centered at the peak emission wavelength of each of the dyes. This filter is switched every few seconds to allow continual monitoring of each of the four fluorophores. For multi wavelength excitation, the optical elements F**3** (excitation filter), DM (dichroic mirror), and F**4** (barrier filter) are switched together. In this manner both the excitation light and the observed emission light are varied. The system in FIG. **7** is a good arrangement for the case of single wavelength excitation. This system has the advantage that no moving parts are required, and fluorescence from all four of the dyes may be simultaneously and continuously monitored. A third approach (iii above) to detection is to elute the labeled molecules at the bottom of the gel, combine them with an agent for excitation of chemiluminescence such as 1,2 dioxetane dione, Gill, S. K. Aldrichimica Acta 16(3), 59–61 (1983); Mellbin, G. J. Liq. Chrom. 6(9), 1603–1616 (1983), and flow the mixture directly into a detector which can measure the emitted light at four separate wavelengths. The background signal in chemiluminescence is much lower than in fluorescence, resulting in higher signal to noise ratios and increased sensitivity. Finally, the measurement may be made by measurements of light absorption (iv above). In this case, a light beam of variable wavelength is passed through the gel, and the decrease in the beam intensity due to absorption of light at the different wavelengths corresponding to the absorption maximum of the four dyes, it is possible to determine which dye molecule is in the light path. As disadvantage of this type of measurement is that absorption measurements are inherently less sensitive than fluorescence measurements.

The above-described detection system is interfaced to a computer **16**. In each time interval examined, the computer **16** receives a signal proportional to the measured signal intensity at that time for each of the four colored tags. This information tells which nucleotide terminates the DNA fragment of the particular length in the observation window at that time. The temporal sequence of colored bands gives the DNA sequence. In FIG. **3** is shown the type of data obtained by conventional methods, as well as the type of data obtained by the improvements described in this invention.

The following Examples are presented solely to illustrate the invention. In the Examples, parts and percentages are by weight unless otherwise indicated.

EXAMPLE I

Gel electrophoresis. Aliquots of the sequencing reactions are combined and loaded onto a 5% polyacrylamide column **10** shown in FIG. **2** from the upper reservoir **12**. The relative amounts of the four different reactions in the mixture are empirically adjusted to give approximately the same fluorescence or absorptive signal intensity from each of the dye DNA conjugates. This permits compensation for differences in dye extinction coefficients, dye fluorescence quantum yields, detector sensitivities and so on. A high voltage is placed across the column **10** so as to electrophorese the labeled DNA fragments through the gel. The labeled DNA segments differing in length by a single nucleotide are separated by electrophoresis in this gel matrix. At or near the bottom of the gel column **10**, the bands of DNA are resolved from one another and pass through the detector **14** (more fully described above). The detector **14** detects the fluorescent or chromophoric bands of DNA in the gel and determines their color, and therefore to which nucleotide they correspond. This information yields the DNA sequence.

EXAMPLE II

FIG. **4** shows a block diagram of a DNA sequenator for use with one dye at a time. The beam (4880 A) from an argon ion laser **100** is passed into the polyacrylamide gel tube (sample) **102** by means of a beamsteerer **104**. Fluorescence exited by the beam is collected using a low f-number lens **106**, passed through an appropriate set of optical filters **108** and **110** to eliminate scattered excitation light and detected using a photomultiplier tube (PMT) **112**. The signal is readily detected on a strip chart recorder. DNA sequencing reactions are carried out utlizing a fluorescein labeled oligonucletide primer. The peaks on the chart correspond to fragments to fluorescein labeled DNA of varying lengths synthesized in the sequencing reactions and separated in the gel tube by electrophoresis. Each peak contains on the order of 10^{-15} to 10^{-16} moles of fluorescein, which is approximately equal to the amount of DNA obtained per band in an equivalent sequencing gel utilizing radioisotope detection. This proves that the fluorescent tag is not removed or degraded from the oligonucleotide primer in the sequencing reactions. It also demonstrates that the detection sensitivity is quite adequate to perform DNA sequence analysis by this means.

Materials

Fluorescein-5-isothiocyanate (FITC) and Texas Red were obtained from Molecular Probes, Inc. (Junction City, Oreg.). tetramethyl rhodamine isothiocyanate (TMRITC) was obtained from Research Organics, Inc. (Cleveland, Ohio.). 4-fluoro-7-nitro-benzofurazan (NBD-fluoride) was obtained from Sigma Chemical Co. (St. Louis, Mo.). Absorption spectra were obtained on a H/P 8491 spectrophotometer. High performance liquid chromatography was performed on a system composed of two Altex 110A pumps, a dual chamber gradient mixer, Rheodyne injector, Kratos 757 UV detector, and an Axxiom 710 controller.

EXAMPLE III

Addition of 5'-aminothymidine phosphoramidites to oligonucleotides.

The protected 5'-aminothymidine phosphoramidites, 5'-(N-9-fluorenylmethyloxycarbonyl)-5'-amino-5'-deoxy-3'-N, N-diisopropylaminomethoxyphosphinyl thymidine, is coupled to the 5'-hydroxyl of an oligonucleotide using well established DNA synthetic procedures. The solvents and reaction conditions used are identical to those used in oligonucleotide synthesis.

EXAMPLE IV

Dye Conjugation

The basic procedure used for the attachment of fluorescent dye molecules to the amino oligonucleotides is to combine the amino oligonucleotide and the dye in aqueous solution buffered to pH 9, to allow the reaction to stand at room temperature for several hours, and then to purify the product in two stages. The first purification step is to remove the bulk of the unreacted or hydrolyzed dye by gel filtration. The second purification stage is to separate the dye conjugate from unreacted oligonucleotide by reverse phase high performance liquid chromatography. Slight variations upon these conditions are employed for the different dyes, and the specific procedures and conditions used for four particular dyes are given below and in Table 1.

TABLE 1

Reverse Phase HPLC Conditions for Dye-oligonucleotide Purification

Sample	Retention time
PLP-15[a]	18'
PLP-15-T-NH_2[b]	18'
FITC PLP-15[c]	27'
NBD PLP-15	25'
TMRITC PLP-15	32' and 34'[d]
Texas Red PLP-15	42'

Retention limes shown are for HPLC gradients of 20% solvent B/80% solvent A to 60% solvent B/40% solvent A in 40 min., where solvent A is 0.1 M triethylammonium acetate pH 7.0 and solvent B is 50% acelonitrile, 50% 0.1 M triethylammonium acetate pH 7.0. The column was an Axxiom ODS 5 micron C 18 column #555-102 available from Cole Scientific, Calabasas, CA. This gradient is not optimized tor purification of PLP-15 and PLP-15-T-NH_2, but the retention times are included for comparison with the dye primer conjugates.

[a]PLP-15 is an oligonucleotide primer for DNA sequence analysis in the M13 vectors. Its sequence is 5'CCC AGT CAC GAC FTT 3'.

[b]PLP-15-T-NH_2 is the oligonucleotide PLP-15 to which a 5'-amino-5'-deoxythymidine base has been added to==at the 5' terminus.

[c]The nomenclature Dye PLP-15 signifies the conjugate of PLP-15-T-NH_2 and the dye molecule.

[d]Two fluorescent oligonucleotide products were obtained with TMRITC. Both were equally effective in sequencing. This is presumed to be due to the two isomers of TMRITC which are present in the commercially available material.

The following procedure is for use with fluorescein isothiocyanate or 4-fluoro-7-nitro-benzofurazan. Amino oligonucleotide (0.1 ml of ~1 mg/ml oligonucleotide in water) is combined with 1 M sodium carbonate/bicarbonate buffer pH 9 (50 µl), 10 mg/ml dye in dimethylformamide (20 µl) and H_2O (80 µl). This mixture is kept in the dark at room temperature for several hours. The mixture is applied to a 10 ml column of Sephadex G-25 (medium) and the colored band of material eluting in the excluded volume is collected. The column is equilibrated and run in water. In control reactions with underivatized oligonucleotides, very little if any dye is associated with the oligonucleotide eluting in the void volume. The colored material is further purified by reverse phase high performance liquid chromatography on an Axxiom C_{18} column (#555-102, Cole Scientific, Calabasas, Calif.) in a linear gradient of acetonitrile:0.1 M triethylammonium acetate, pH 7.0. It is convenient for this separation to run the column eluant through both a UV detector (for detecting the DNA absorbance) and a fluorescence detector (for detecting the dye moiety). The desired product is a peak on the chromatogram which is both strongly UV absorbing and strongly fluorescent. The dye oligonucleotide conjugates elute at higher acetonitrile concentrations than the oligonucleotides alone, as shown in Table 1. The oligonucleotide is obtained from the high performance liquid chromatographyin solution in a mixture of acetonitrile and 0.1 M triethylammonium acetate buffer. This is removed by lyophilization and the resulting material is redissolved by vortexing in 10 mM sodium hydroxzide (for a minimum amount of time) followed by neutralization with a five fold molar excess (to sodium hydroxide) of Tris buffer, pH 7.5.

The conjugation with Texas Red is identical to that described for fluorescein isothiocyanate and 4-fluoro-7-nitro-benzofurazan, except that:

a) prior to separation on Sephadex G-25 the reaction is made 1 M in ammonium acetate and kept at room temperature for 30 minutes, and

b) the Sephadex G-25 column is run in 0.1 M ammonium acetate. This largely eliminates nonspecific binding of the dye molecule to the oligonucleotide.

The conjugation with tetramethyl rhodamine isothiocyanate cyanate is identical to that for Texas Red except that the reaction-is carried out in 10 mM sodium carbonate/bicarbonate buffer, pH 9.0, and 50% dioxane. This increases solubility of the tetramethyl rhodamine and a much higher yield of dye oligonucleotide conjugate is obtained.

In some cases, particularly with the rhodamine-like dyes, a substantial amount of nonspecific binding of dye was observed, as manifested by an inappropriately large dye absorption present in the material eluted from the gel filtration column. In these cases the material was concentrated and reapplied to a second gel filtration column prior to high performance liquid chromatography purification. This generally removed the majority of the noncovalently associated dye.

EXAMPLE V

Properties of Dye-Oligonucleotide Conjugates

The development of chemistry for the synthesis of dye oligonucleotide conjugates allows their use as primers in DNA sequence analysis. Various fluorescent dye primers have been tested by substituting them for the normal primer in DNA sequence analysis by the enzymatic method. An autoradiogram of a DNA sequencing gel in which these dye-conjugated primers were utilized in T reactions in place of the normal oligonucleotide primer was prepared. This autoradiogram was obtained by conventional methods employing α-^{32}P-dCTP as a radiolabel. The autoradiogram showed that the underivitized primer, amino-derivitized primer, and dye conjugated primers all give the same pattern of bands (corresponding to the DNA sequence), indicating that the deriv-

itized primers retain their ability to hybridize specifically to the complementary strand. Secondly, the bands generated using the different primers differ in their mobilities, showing that it is indeed the dye-primers which are responsible for the observed pattern, and not a contaminant of unreacted or underivitized oligonucleotide. Thirdly, the intensity of the bands obtained with the different primers is comparable, indicating that the strength of hybridization is not significantly perturbed by the presence of the dye molecules.

The separations are again carried out in an acrylamide gel column. The beam from an argon ion laser is passed into the polyacrylamide gel tube (sample) by means of a beamsteerer. Fluorescence exited by the beam is collected using a low f-number lens, passed through an appropriate set of optical filters to eliminate scattered excitation light and detected using a photomultiplier tube (PMT). The signal is monitored on a strip chart recorder. DNA sequencing reactions have been carried out utilizing each of the four different dye coupled oligonucleotide primers. In each case a series of peaks are observed on the chart paper. The peaks correspond to fragments of dye labeled DNA of varying lengths synthesized in the sequencing reactions and separated in the gel tube by electrophoresis. Each peak contains of the order of 10^{-14} to 10^{-16} moles of dye, which is approximately equal to the amount of DNA obtained per band in an equivalent sequencing gel utilizing radioisotope detection. This proves that the fluorescent tag is not removed or degraded from the oligonucleotide primer in the sequencing reactions. It also demonstrates that the detection sensitivity is quite adequate to perform DNA sequence analysis by this means, and that adequate resolution of the DNA fragments is obtained in a tube gel system.

Having fully described the invention it is intended that it be limited only by the lawful scope of the appended claims.

What is claimed is:

[1. A duplex comprising an oligonucleotide primer and a template, wherein the primer is covalently coupled to a chromophore or fluorophore so as to allow chain extension by a polymerase.]

[2. A duplex comprising an extended oligonucleotide primer and a template, produced by providing a duplex according to claim 1 and extending the oligonucleotide primer with a polymerase.]

[3. A single-stranded labeled polynucleotide produced by separating the extended oligonucleotide primer from the duplex of claim 2.]

[4. A set of duplexes comprising two or more of the duplexes of claim 1.]

[5. A set of duplexes comprising two or more of the duplexes of claim 2.]

[6. A set of polynucleotides comprising two or more single-stranded labeled polynucleotides of claim 3.]

[7. A set of reagents comprising oligonucleotide primers covalently coupled to one or more chromophores or fluorophores so as to allow chain extension by a polymerase, and a polymerase.]

[8. A single-stranded labeled polynucleotide comprising a first portion and a second portion,

wherein the first portion comprises an oligonucleotide primer covalently coupled to a chromophore or fluorophore; and

wherein the second portion is produced by extension of the first portion along a complementary template.]

[9. The polynucleotide of claim 8, wherein the chromophore or fluorophore is covalently coupled to the first portion through an amine linkage.]

[10. The polynucleotide of claim 8, wherein the chromophore or fluorophore is covalently coupled to the first portion at its 5' end.]

[11. The duplex of claim 1, prepared by a method comprising hybridizing an oligonucleotide primer to a template, wherein the primer is covalently coupled to a chromophore or fluorophore so as to allow chain extension by a polymerase.]

[12. The duplex of claim 11, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[13. The duplex of claim 11, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[14. A single-stranded labeled polynucleotide produced by the method comprising the steps of extending the oligonucleotide primer of the duplex of claim 1 by a polymerase to produce a labeled polynucleotide and separating the labeled polynucleotide from the template.]

[15. The polynucleotide of claim 14, wherein the chromophore or fluorophore is covalently coupled to the oligonucleotide through an amine linkage.]

[16. The polynucleotide of claim 14, wherein the chromophore or fluorophore is covalently coupled to the oligonucleotide at its 5' end.]

[17. A chain termination DNA sequencing method comprising extending the primer of the duplex of claim 1 by a polymerase to produce a labeled polynucleotide, and separating the labeled polynucleotide from the template.]

[18. A chain termination DNA sequencing method comprising extending the primers of the set of duplexes of claim 4 by a polymerase to produce a set of labeled polynucleotides.]

[19. The chain termination DNA sequencing method of claim 18, wherein the set of duplexes comprises four DNA sequencing reactions, wherein each labeled polynucleotide is distinguishable by spectral characteristics of the chromophore or fluorophore covalently coupled thereto.]

[20. The oligonucleotide primer of claim 1, wherein the primer is DNA.]

[21. The oligonucleotide primer of claim 1 wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[22. The duplex of either of claim 1 or 2, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[23. The set of duplexes of either of claim 4 or 5, wherein the primers are DNA.]

[24. The set of duplexes of either of claim 4 or 5, wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[25. The set of duplexes of either of claim 4 or 5, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[26. The set of reagents of claim 7, wherein the primers are DNA.]

[27. The set of reagents of claim 7, wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[28. The set of reagents of claim 7, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[29. The polynucleotide of any of claims 14 to 16, wherein the primer is DNA.]

[30. The polynucleotide of any of claims 14 to 16, wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[31. The polynucleotide of any of claims 14 to 16, wherein the chromophore or fluorophore is detectable by exposure tc a laser.]

[32. The duplex of any of claims 11 to 13, wherein the primer is DNA.]

[33. The duplex of any of claims 11 to 13, wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[34. The duplex of any of claims 11 to 13, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[35. The duplex of either of claim 1 or 2, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[36. The set of duplexes of either of claim 4 or 5, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[37. The set of reagents of claim 7, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[38. The duplex of either of claim 1 or 2, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[39. The set of duplexes of either of claim 4 or 5, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[40. The set of reagents of claim 7, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[41. The polynucleotide of claim 3, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[42. The polynucleotide of claim 3, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[43. The polynucleotide of claim 3, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[44. The set of polynucleotides of claim 6, wherein the primers are DNA.]

[45. The set of polynucleotides of claim 6, wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[46. The set of polynucleotides of claim 6, wherein the chromophore or fluorophore is detectable by exposure to a laser.]

[47. The set of polynucleotides of claim 6, wherein the chromophore or fluorophore is covalently coupled to the primer through an amine linkage.]

[48. The set of polynucleotides of claim 6, wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[49. A duplex comprising an oligonucleotide primer and a template, wherein the primer hybridizes to a specific region of the template and wherein the primer is covalently coupled to a chromophore or fluorophore so as to allow chain extension by a polymerase.]

[50. A plurality of identical oligonucleotide primers of defined length and base sequences wherein each primer is covalently coupled to a fluorophore or chromophore so as to allow chain extension by a polymerase.]

[51. The plurality of claim 50 wherein said primers have a free 3' hydroxyl group.]

[52. The plurality of claim 51 wherein the chromophore or fluorophore is covalently coupled to the primer at its 5' end.]

[53. The plurality of claim 50 wherein said primers are coupled to said fluorophore or chromophore by an amine linkage.]

[54. A composition comprising the plurality of claim 50.]

[55. The composition of claim 54 further comprising a buffer.]

[56. A set of reagents comprising the plurality of claim 50 and a polymerase.]

[57. A set of reagents comprising two or more pluralities of oligonucleotide primers of claim SO wherein each plurality has a different emission spectra.]

[58. A plurality of single-stranded labeled polynucleotides produced by the method comprising the steps of hybridizing the plurality of oligonucleotide primers of claim 50 to a template thereby forming a plurality of duplexes; extending the primers of said duplexes by a polymerase thereby forming labeled polynucleotides; and separating said labeled polynucleotides from said duplexes.]

[59. A set of single stranded labeled polynucleotides comprising two or more pluralities of polynucleotides of claim 58, wherein each plurality has a different emission spectra.]

[60. The plurality of claim 50 wherein the chromophore or fluorophore is detectable by exposure to a high-intensity monochromatic light source.]

[61. The plurality of claim 50 wherein the chromophore or fluorophore is detectable by exposure to a laser.]

62. A method of nucleic acid sequence analysis, comprising extending an oligonucleotide along a complementary strand of DNA of a duplex by a polymerase to produce a labeled extension product, wherein the duplex comprises the oligonucleotide specifically hybridized to the complementary strand of DNA, and wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

63. The method of claim 62, further comprising separating said labeled extension product from said duplex.

64. A DNA sequencing method, comprising

extending oligonucleotides of a set of duplexes along hybridized complementary strands of DNA by a polymerase to produce a set of labeled extension products, wherein the set of labeled extension products comprises two or more extension products, wherein an extension product comprises an extended oligonucleotide specifically hybridized to a complementary strand of DNA,

thereby producing four sets of labeled extension products, wherein the extension products of each set are distinguishably labeled with a different type of fluorophore from the extension products of the other sets.

65. The method of claim 64 or claim 62, wherein the fluorophore is covalently coupled to the oligonucleotide through an amine linkage.

66. A mixture comprising a polymerase and a duplex, wherein the duplex comprises an oligonucleotide specifically hybridized to a complementary strand of DNA, wherein the oligonucleotide is covalently coupled to a fluorophore so as to allow chain extension by the polymerase.

67. A composition comprising four sets of oligonucleotides, wherein oligonucleotides of each of the four sets are distinguishably labeled with a different type of fluorophore from the oligonucleotides of the other three sets.

68. The method of claim 64, wherein the extension products comprise a terminal nucleotide having any one of four different types of terminal base components, wherein substantially all molecules of the same set of labeled extension products have the same type of terminal base component, and substantially all molecules of different sets of labeled extension products have different types of terminal base components.

69. The composition of claim 67, wherein the oligonucleotides comprise a terminal nucleotide having any one of four different types of terminal base components, wherein substantially all oligonucleotide molecules of the same set have the

same type of terminal base component, and substantially all oligonucleotide molecules of different sets have different types of terminal base components.

70. The method of claim 62, wherein substantially all molecules of the labeled extension product individually comprise a single fluorescent nucleotide.

71. The method of claim 64, wherein substantially all molecules of the labeled extension products individually comprise a single fluorescent nucleotide.

72. The mixture of claim 66, wherein substantially all oligonucleotide molecules individually comprise a single fluorescent nucleotide.

73. The composition of claim 67, wherein substantially all oligonucleotide molecules of each set individually comprise a single fluorescent nucleotide.

74. The method of claim 62, wherein substantially all molecules of the labeled extension product are individually coupled to a fluorophore by a single covalent linkage.

75. The method of claim 64, wherein substantially all molecules of the labeled extension products are individually coupled to a fluorophore by a single covalent linkage.

76. The mixture of claim 66, wherein substantially all oligonucleotide molecules are individually coupled to a fluorophore by a single covalent linkage.

77. The composition of claim 67, wherein substantially all oligonucleotide molecules of each set are individually coupled to a fluorophore by a single covalent linkage.

78. The method of claim 68, wherein substantially all molecules of the labeled extension products individually comprise a single fluorescent nucleotide.

79. The composition of claim 69, wherein substantially all oligonucleotide molecules of each set individually comprise a single fluorescent nucleotide.

80. The method of claim 74, wherein substantially all molecules of the labeled extension product individually are terminally labeled with a fluorophore.

81. The method of claim 75, wherein substantially all molecules of the labeled extension products individually are terminally labeled with a fluorophore.

82. The mixture of claim 76, wherein substantially all oligonucleotide molecules individually are terminally labeled with a fluorophore.

83. The composition of claim 77, wherein substantially all oligonucleotide molecules of each set individually are terminally labeled with a fluorophore.

84. The method of claim 68, wherein substantially all molecules of the labeled extension products individually are terminally labeled with a fluorophore.

85. The composition of claim 69, wherein substantially all oligonucleotide molecules of each set individually are terminally labeled with a fluorophore.

86. The method of claim 70, wherein substantially all molecules of the labeled extension product individually are terminally labeled with a fluorophore.

87. The method of claim 71, wherein substantially all molecules of the labeled extension products individually are terminally labeled with a fluorophore.

88. The mixture of claim 72, wherein substantially all oligonucleotide molecules individually are terminally labeled with a fluorophore.

89. The composition of claim 73, wherein substantially all oligonucleotide molecules of each set individually are terminally labeled with a fluorophore.

90. The method of claim 78, wherein substantially all molecules of the labeled extension products individually are terminally labeled with a fluorophore.

91. The composition of claim 79, wherein substantially all oligonucleotide molecules of each set individually are terminally labeled with a fluorophore.

92. The method of claim 74, wherein substantially all molecules of the labeled extension product individually comprise a 5' terminal fluorescent nucleotide.

93. The method of claim 75, wherein substantially all molecules of the labeled extension products individually comprise a 5' terminal fluorescent nucleotide.

94. The mixture of claim 76, wherein substantially all oligonucleotide molecules individually comprise a 5' terminal fluorescent nucleotide.

95. The composition of claim 77, wherein substantially all oligonucleotide molecules of each set individually comprise a 5' terminal fluorescent nucleotide.

96. The method of claim 84, wherein substantially all molecules of the labeled extension products individually comprise a 5' terminal fluorescent nucleotide.

97. The composition of claim 85, wherein substantially all oligonucleotide molecules of each set individually comprise a 5' terminal fluorescent nucleotide.

98. The method of claim 86, wherein substantially all molecules of the labeled extension product individually comprise a 5' terminal fluorescent nucleotide.

99. The method of claim 87, wherein substantially all molecules of the labeled extension products individually comprise a 5' terminal fluorescent nucleotide.

100. The mixture of claim 88, wherein substantially all oligonucleotide molecules individually comprise a 5' terminal fluorescent nucleotide.

101. The composition of claim 89, wherein substantially all oligonucleotide molecules of each set individually comprise a 5' terminal fluorescent nucleotide.

102. The method of claim 90, wherein substantially all molecules of the labeled extension products individually comprise a 5' terminal fluorescent nucleotide.

103. The composition of claim 91, wherein substantially all oligonucleotide molecules of each set individually comprise a 5' terminal fluorescent nucleotide.

104. The composition of claim 69, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal fluorescent nucleotide.

105. The composition of claim 73, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal fluorescent nucleotide.

106. The composition of claim 79, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal fluorescent nucleotide.

107. The method of claim 68, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

108. The composition of claim 69, wherein substantially all oligonucleotide molecules of each set individually (i) are specifically hybridized to a complementary strand of DNA, and (ii) comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

109. The method of claim 71, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

110. The composition of claim 73, wherein substantially all oligonucleotide molecules of each set individually (i) are specifically hybridized to a complementary strand of DNA,

and (ii) comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

111. The method of claim 75, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

112. The composition of claim 77, wherein substantially all oligonucleotide molecules of each set individually (i) are specifically hybridized to a complementary strand of DNA, and (ii) comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

113. The composition of claim 79, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide in a complementary strand of DNA.

114. The method of claim 81, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

115. The composition of claim 83, wherein substantially all oligonucleotide molecules of each set individually (i) are specifically hybridized to a complementary strand of DNA, and (ii) comprise a 3' terminal nucleotide that is complementary to a corresponding nucleotide on the complementary strand of DNA.

116. The method of claim 68, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

117. The composition of claim 69, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

118. The method of claim 70, wherein substantially all molecules of the labeled extension product individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

119. The method of claim 71, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

120. The composition of claim 73, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

121. The method of claim 74, wherein substantially all molecules of the labeled extension product individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

122. The method of claim 75, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

123. The composition of claim 77, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

124. The method of claim 78, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

125. The composition of claim 79, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

126. The method of claim 80, wherein substantially all molecules of the labeled extension product individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

127. The method of claim 81, wherein substantially all molecules of the labeled extension products individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

128. The composition of claim 83, wherein substantially all oligonucleotide molecules of each set individually comprise a 3' terminal nucleotide that is adapted to terminate polymerase extension.

129. The composition of claim 69, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

130. The composition of claim 73, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

131. The composition of claim 77, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

132. The composition of claim 79, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

133. The composition of claim 83, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

134. The composition of claim 85, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

135. The composition of claim 89, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

136. The composition of claim 91, further comprising a polymerase or nucleotides adapted to terminate polymerase extension.

137. The method of claim 68, wherein the four different types of terminal base components are adenosine, guanosine, thymidine and cytosine.

138. The composition of claim 69, wherein the four different types of terminal base components are adenosine, guanosine, thymidine and cytosine.

139. The method of claim 81, wherein the oligonucleotides are fluorescently labeled before being extended.

140. The method of claim 84, wherein the oligonucleotides are fluorescently labeled before being extended.

141. The method of claim 87, wherein the oligonucleotides are fluorescently labeled before being extended.

142. The method of claim 90, wherein the oligonucleotides are fluorescently labeled before being extended.

143. A method of nucleic acid sequence analysis, comprising producing the composition of claim 69, and detecting the type of fluorophore on oligonucleotides of the composition.

144. A method of nucleic acid sequence analysis, comprising producing the composition of claim 73, and detecting the type of fluorophore on oligonucleotides of the composition.

145. A method of nucleic acid sequence analysis, comprising producing the composition of claim 77, and detecting the type of fluorophore on oligonucleotides of the composition.

146. A method of nucleic acid sequence analysis, comprising producing the composition of claim 83, and detecting the type of fluorophore on oligonucleotides of the composition.

147. A method of nucleic acid sequence analysis, comprising producing the composition of claim 85, and detecting the type of fluorophore on oligonucleotides of the composition.

148. A method of nucleic acid sequence analysis, comprising producing the composition of claim 104, and detecting the type of fluorophore on oligonucleotides of the composition.

149. A method of nucleic acid sequence analysis, comprising producing the composition of claim 105, and detecting the type of fluorophore on oligonucleotides of the composition.

150. A method of nucleic acid sequence analysis, comprising producing the composition of claim 108, and detecting the type of fluorophore on oligonucleotides of the composition.

151. A method of nucleic acid sequence analysis, comprising producing the composition of claim 117, and detecting the type of fluorophore on oligonucleotides of the composition.

152. The method of claim 68, wherein the oligonucleotides are fluorescently labeled before being extended.

153. The method of claim 71, wherein the oligonucleotides are fluorescently labeled before being extended.

154. The method of claim 75, wherein the oligonucleotides are fluorescently labeled before being extended.

155. The method of claim 78, wherein the oligonucleotides are fluorescently labeled before being extended.

156. The method of claim 93, wherein the oligonucleotides are fluorescently labeled before being extended.

157. The method of claim 107, wherein the oligonucleotides are fluorescently labeled before being extended.

158. The method of claim 116, wherein the oligonucleotides are fluorescently labeled before being extended.

* * * * *

TAB 8

notes under sections 32, 102, and 111 of this title], the amendments made by this section shall take effect upon the expiration of the 18-month period beginning on the date of the enactment of this Act [Sept. 16, 2011], and shall apply to any application for patent, and to any patent issuing thereon, that contains or contained at any time—

''(A) a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after the effective date described in this paragraph; or

''(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim.

''(2) INTERFERING PATENTS.—The provisions of sections 102(g), 135, and 291 of title 35, United States Code, as in effect on the day before the effective date set forth in paragraph (1) of this subsection, shall apply to each claim of an application for patent, and any patent issued thereon, for which the amendments made by this section also apply, if such application or patent contains or contained at any time—

''(A) a claim to an invention having an effective filing date as defined in section 100(i) of title 35, United States Code, that occurs before the effective date set forth in paragraph (1) of this subsection; or

''(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim.''

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective Nov. 29, 1999, and applicable to any patent issuing from an original application filed in the United States on or after that date, see section 1000(a)(9) [title IV, §4608(a)] of Pub. L. 106–113, set out as a note under section 41 of this title.

§ 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(July 19, 1952, ch. 950, 66 Stat. 797.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., §31 (R.S. 4886, amended (1) Mar. 3, 1897, ch. 391, §1, 29 Stat. 692, (2) May 23, 1930, ch. 312, §1, 46 Stat. 376, (3) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212).

The corresponding section of existing statute is split into two sections, section 101 relating to the subject matter for which patents may be obtained, and section 102 defining statutory novelty and stating other conditions for patentability.

Section 101 follows the wording of the existing statute as to the subject matter for patents, except that reference to plant patents has been omitted for incorporation in section 301 and the word ''art'' has been replaced by ''process'', which is defined in section 100. The word ''art'' in the corresponding section of the existing statute has a different meaning than the same word as used in other places in the statute; it has been interpreted by the courts as being practically synonymous with process or method. ''Process'' has been used as its meaning is more readily grasped than ''art'' as interpreted, and the definition in section 100(b) makes it clear that ''process or method'' is meant. The remainder of the definition clarifies the status of processes or methods which involve merely the new use of a known process, machine, manufacture, composition of matter, or material; they are processes or methods under the statute and may be patented provided the conditions for patentability are satisfied.

LIMITATION ON ISSUANCE OF PATENTS

Pub. L. 112–29, §33, Sept. 16, 2011, 125 Stat. 340, provided that:

''(a) LIMITATION.—Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism.

''(b) EFFECTIVE DATE.—

''(1) IN GENERAL.—Subsection (a) shall apply to any application for patent that is pending on, or filed on or after, the date of the enactment of this Act [Sept. 16, 2011].

''(2) PRIOR APPLICATIONS.—Subsection (a) shall not affect the validity of any patent issued on an application to which paragraph (1) does not apply.''

§ 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language;[1] or

(f) he did not himself invent the subject matter sought to be patented, or

(g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

[1] So in original. The semicolon probably should be a comma.

(July 19, 1952, ch. 950, 66 Stat. 797; Pub. L. 92–358, §2, July 28, 1972, 86 Stat. 502; Pub. L. 94–131, §5, Nov. 14, 1975, 89 Stat. 691; Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §§4505, 4806], Nov. 29, 1999, 113 Stat. 1536, 1501A–565, 1501A–590; Pub. L. 107–273, div. C, title III, §13205(1), Nov. 2, 2002, 116 Stat. 1902; Pub. L. 112–29, §3(b)(1), Sept. 16, 2011, 125 Stat. 285.)

AMENDMENT OF SECTION

Pub. L. 112–29, §3(b)(1), (n), Sept. 16, 2011, 125 Stat. 285, 293, provided that, effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, this section is amended to read as follows:

§102. Conditions for patentability; novelty

(a) Novelty; Prior Art.—A person shall be entitled to a patent unless—

(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or

(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

(b) Exceptions.—

(1) Disclosures made 1 year or less before the effective filing date of the claimed invention.—A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if—

(A) the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(B) the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

(2) Disclosures appearing in applications and patents.—A disclosure shall not be prior art to a claimed invention under subsection (a)(2) if—

(A) the subject matter disclosed was obtained directly or indirectly from the inventor or a joint inventor;

(B) the subject matter disclosed had, before such subject matter was effectively filed under subsection (a)(2), been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(C) the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person.

(c) Common Ownership Under Joint Research Agreements.—Subject matter disclosed and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person in applying the provisions of subsection (b)(2)(C) if—

(1) the subject matter disclosed was developed and the claimed invention was made by, or on behalf of, 1 or more parties to a joint research agreement that was in effect on or before the effective filing date of the claimed invention;

(2) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(3) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(d) Patents and Published Applications Effective as Prior Art.—For purposes of determining whether a patent or application for patent is prior art to a claimed invention under subsection (a)(2), such patent or application shall be considered to have been effectively filed, with respect to any subject matter described in the patent or application—

(1) if paragraph (2) does not apply, as of the actual filing date of the patent or the application for patent; or

(2) if the patent or application for patent is entitled to claim a right of priority under section 119, 365(a), or 365(b), or to claim the benefit of an earlier filing date under section 120, 121, or 365(c), based upon 1 or more prior filed applications for patent, as of the filing date of the earliest such application that describes the subject matter.

See 2011 Amendment note below.

HISTORICAL AND REVISION NOTES

Paragraphs (a), (b), and (c) are based on Title 35, U.S.C., 1946 ed., §31 (R.S. 4886, amended (1) Mar. 3, 1897, ch. 391, §1, 29 Stat. 692, (2) May 23, 1930, ch. 312, §1, 46 Stat. 376, (3) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212).

No change is made in these paragraphs other than that due to division into lettered paragraphs. The interpretation by the courts of paragraph (a) as being more restricted than the actual language would suggest (for example, ''known'' has been held to mean ''publicly known'') is recognized but no change in the language is made at this time. Paragraph (a) together with section 104 contains the substance of Title 35, U.S.C., 1946 ed., §72 (R.S. 4923).

Paragraph (d) is based on Title 35, U.S.C., 1946 ed., §32, first paragraph (R.S. 4887 (first paragraph), amended (1) Mar. 3, 1897, ch. 391, §3, 29 Stat. 692, 693, (2) Mar. 3, 1903, ch. 1019, §1, 32 Stat. 1225, 1226, (3) June 19, 1936, ch. 594, 49 Stat. 1529).

The section has been changed so that the prior foreign patent is not a bar unless it was granted before the filing of the application in the United States.

Paragraph (e) is new and enacts the rule of *Milburn* v. *Davis-Bournonville*, 270 U.S. 390, by reason of which a United States patent disclosing an invention dates from the date of filing the application for the purpose of anticipating a subsequent inventor.

Paragraph (f) indicates the necessity for the inventor as the party applying for patent. Subsequent sections permit certain persons to apply in place of the inventor under special circumstances.

Paragraph (g) is derived from Title 35, U.S.C., 1946 ed., §69 (R.S. 4920, amended (1) Mar. 3, 1897, ch. 391, §2, 29 Stat. 692, (2) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212), the second defense recited in this section. This paragraph retains the present rules of law governing the determination of priority of invention.

Language relating specifically to designs is omitted for inclusion in subsequent sections.

AMENDMENTS

2011—Pub. L. 112–29 amended section generally. Prior to amendment, section related to conditions for patentability; novelty and loss of right to patent.

2002—Subsec. (e). Pub. L. 107–273, amended Pub. L. 106–113, § 1000(a)(9) [title IV, § 4505]. See 1999 Amendment note below. Prior to being amended by Pub. L. 107–273, Pub. L. 106–113, § 1000(a)(9) [title IV, § 4505], had amended subsec. (e) to read as follows: ''The invention was described in—

''(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

''(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a); or''.

1999—Subsec. (e). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4505], as amended by Pub. L. 107–273, amended subsec. (e) generally. Prior to amendment, subsec. (e) read as follows: ''the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or''.

Subsec. (g). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4806], amended subsec. (g) generally. Prior to amendment, subsec. (g) read as follows: ''before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.''

1975—Par. (e). Pub. L. 94–131 inserted provision for nonentitlement to a patent where the invention was described in a patent granted on an international application by another who has fulfilled the requirements of pars. (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

1972—Subsec. (d). Pub. L. 92–358 inserted reference to inventions that were the subject of an inventors' certificate.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by Pub. L. 112–29 effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, § 4505] of Pub. L. 106–113 effective Nov. 29, 2000 and applicable to all patents and all applications for patents pending on or filed after Nov. 29, 2000, see section 1000(a)(9) [title IV, § 4508] of Pub. L. 106–113, as amended, set out as a note under section 10 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

EFFECTIVE DATE OF 1972 AMENDMENT

Section 3(b) of Pub. L. 92–358 provided that: ''Section 2 of this Act [amending this section] shall take effect six months from the date when Articles 1 to 12 of the Paris Convention of March 20, 1883, for the Protection of Industrial Property, as revised at Stockholm, July 14, 1967, come into force with respect to the United States [Aug. 25, 1973] and shall apply to applications thereafter filed in the United States.''

SAVINGS PROVISIONS

Provisions of subsec. (g) of this section as in effect on the day before the expiration of the 18-month period beginning on Sept. 16, 2011, apply to each claim of certain applications for patent, and certain patents issued thereon, for which the amendments made by section 3 of Pub. L. 112–29 also apply, see section 3(n)(2) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

Section 4 of act July 19, 1952, ch. 950, 66 Stat. 815, provided that subsec. (d) of this section should not apply to existing patents and pending applications, but that the law previously in effect, namely the first paragraph of R.S. 4887 [first paragraph of section 32 of former Title 35], should apply to such patents and applications. Said paragraph of section 32 provided that:

''No person otherwise entitled thereto shall be debarred from receiving a patent for his invention or discovery, nor shall any patent be declared invalid by reason of its having been first patented or caused to be patented by the inventor or his legal representatives or assigns in a foreign country, unless the application for said foreign patent was filed more than twelve months, in cases within the provisions of section 31 of this title, and six months in cases of designs, prior to the filing of the application in this country, in which case no patent shall be granted in this country.''

CONTINUITY OF INTENT UNDER THE CREATE ACT

Pub. L. 112–29, § 3(b)(2), Sept. 16, 2011, 125 Stat. 287, provided that: ''The enactment of section 102(c) of title 35, United States Code, under paragraph (1) of this subsection is done with the same intent to promote joint research activities that was expressed, including in the legislative history, through the enactment of the Cooperative Research and Technology Enhancement Act of 2004 (Public Law 108–453; the 'CREATE Act') [see Short Title of 2004 Amendment note set out under section 1 of this title], the amendments of which are stricken by subsection (c) of this section [amending section 103 of this title]. The United States Patent and Trademark Office shall administer section 102(c) of title 35, United States Code, in a manner consistent with the legislative history of the CREATE Act that was relevant to its administration by the United States Patent and Trademark Office.''

TAX STRATEGIES DEEMED WITHIN THE PRIOR ART

Pub. L. 112–29, § 14, Sept. 16, 2011, 125 Stat. 327, provided that:

''(a) IN GENERAL.—For purposes of evaluating an invention under section 102 or 103 of title 35, United States Code, any strategy for reducing, avoiding, or deferring tax liability, whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.

''(b) DEFINITION.—For purposes of this section, the term 'tax liability' refers to any liability for a tax under any Federal, State, or local law, or the law of any foreign jurisdiction, including any statute, rule, regulation, or ordinance that levies, imposes, or assesses such tax liability.

''(c) EXCLUSIONS.—This section does not apply to that part of an invention that—

''(1) is a method, apparatus, technology, computer program product, or system, that is used solely for preparing a tax or information return or other tax filing, including one that records, transmits, transfers, or organizes data related to such filing; or

''(2) is a method, apparatus, technology, computer program product, or system used solely for financial management, to the extent that it is severable from any tax strategy or does not limit the use of any tax strategy by any taxpayer or tax advisor.

''(d) RULE OF CONSTRUCTION.—Nothing in this section shall be construed to imply that other business methods are patentable or that other business method patents are valid.

''(e) EFFECTIVE DATE; APPLICABILITY.—This section shall take effect on the date of the enactment of this Act [Sept. 16, 2011] and shall apply to any patent application that is pending on, or filed on or after, that date, and to any patent that is issued on or after that date.''

EMERGENCY RELIEF FROM POSTAL SITUATION AFFECTING PATENT CASES

Relief as to filing date of patent application or patent affected by postal situation beginning on Mar. 18, 1970, and ending on or about Mar. 30, 1970, but patents issued with earlier filing dates not effective as prior art under subsec. (e) of this section as of such earlier filing dates, see section 1(a) of Pub. L. 92–34, formerly set out in a note under section 111 of this title.

§ 103. Conditions for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(b)(1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious if—

(A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and

(B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.

(2) A patent issued on a process under paragraph (1)—

(A) shall also contain the claims to the composition of matter used in or made by that process, or

(B) shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent, notwithstanding section 154.

(3) For purposes of paragraph (1), the term ''biotechnological process'' means—

(A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to—

(i) express an exogenous nucleotide sequence,

(ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or

(iii) express a specific physiological characteristic not naturally associated with said organism;

(B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and

(C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).

(c)(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if—

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(3) For purposes of paragraph (2), the term ''joint research agreement'' means a written contract, grant, or cooperative agreement entered into by two or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 98–622, title I, § 103, Nov. 8, 1984, 98 Stat. 3384; Pub. L. 104–41, § 1, Nov. 1, 1995, 109 Stat. 351; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4807(a)], Nov. 29, 1999, 113 Stat. 1536, 1501A–591; Pub. L. 108–453, § 2, Dec. 10, 2004, 118 Stat. 3596; Pub. L. 112–29, §§ 3(c), 20(j), Sept. 16, 2011, 125 Stat. 287, 335.)

AMENDMENT OF SECTION

Pub. L. 112–29, § 20(j), (l), Sept. 16, 2011, 125 Stat. 335, provided that, effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, this section is amended by striking ''of this title'' each place that term appears. See 2011 Amendment notes below.

Pub. L. 112–29, § 3(c), (n), Sept. 16, 2011, 125 Stat. 287, 293, provided that, effective upon the

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''(c) EXCLUSIONS.—This section does not apply to that part of an invention that—

''(1) is a method, apparatus, technology, computer program product, or system, that is used solely for preparing a tax or information return or other tax filing, including one that records, transmits, transfers, or organizes data related to such filing; or

''(2) is a method, apparatus, technology, computer program product, or system used solely for financial management, to the extent that it is severable from any tax strategy or does not limit the use of any tax strategy by any taxpayer or tax advisor.

''(d) RULE OF CONSTRUCTION.—Nothing in this section shall be construed to imply that other business methods are patentable or that other business method patents are valid.

''(e) EFFECTIVE DATE; APPLICABILITY.—This section shall take effect on the date of the enactment of this Act [Sept. 16, 2011] and shall apply to any patent application that is pending on, or filed on or after, that date, and to any patent that is issued on or after that date.''

EMERGENCY RELIEF FROM POSTAL SITUATION AFFECTING PATENT CASES

Relief as to filing date of patent application or patent affected by postal situation beginning on Mar. 18, 1970, and ending on or about Mar. 30, 1970, but patents issued with earlier filing dates not effective as prior art under subsec. (e) of this section as of such earlier filing dates, see section 1(a) of Pub. L. 92–34, formerly set out in a note under section 111 of this title.

§ 103. Conditions for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(b)(1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious if—

(A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and

(B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.

(2) A patent issued on a process under paragraph (1)—

(A) shall also contain the claims to the composition of matter used in or made by that process, or

(B) shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent, notwithstanding section 154.

(3) For purposes of paragraph (1), the term ''biotechnological process'' means—

(A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to—

(i) express an exogenous nucleotide sequence,

(ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or

(iii) express a specific physiological characteristic not naturally associated with said organism;

(B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and

(C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).

(c)(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if—

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(3) For purposes of paragraph (2), the term ''joint research agreement'' means a written contract, grant, or cooperative agreement entered into by two or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 98–622, title I, § 103, Nov. 8, 1984, 98 Stat. 3384; Pub. L. 104–41, § 1, Nov. 1, 1995, 109 Stat. 351; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4807(a)], Nov. 29, 1999, 113 Stat. 1536, 1501A–591; Pub. L. 108–453, § 2, Dec. 10, 2004, 118 Stat. 3596; Pub. L. 112–29, §§ 3(c), 20(j), Sept. 16, 2011, 125 Stat. 287, 335.)

AMENDMENT OF SECTION

Pub. L. 112–29, § 20(j), (l), Sept. 16, 2011, 125 Stat. 335, provided that, effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, this section is amended by striking ''of this title'' each place that term appears. See 2011 Amendment notes below.

Pub. L. 112–29, § 3(c), (n), Sept. 16, 2011, 125 Stat. 287, 293, provided that, effective upon the

expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, this section is amended to read as follows:

§ 103. Conditions for patentability; non-obvious subject matter

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

See 2011 Amendment notes below.

HISTORICAL AND REVISION NOTES

There is no provision corresponding to the first sentence explicitly stated in the present statutes, but the refusal of patents by the Patent Office, and the holding of patents invalid by the courts, on the ground of lack of invention or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.

The second sentence states that patentability as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius.

AMENDMENTS

2011—Pub. L. 112–29, § 3(c), amended section generally. Prior to amendment, section consisted of subsecs. (a) to (c) and related to conditions for patentability; non-obvious subject matter.

Subsecs. (a), (c)(1). Pub. L. 112–29, § 20(j), struck out ''of this title'' after ''102''.

2004—Subsec. (c). Pub. L. 108–453 amended subsec. (c) generally. Prior to amendment, subsec. (c) read as follows: ''Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.''

1999—Subsec. (c). Pub. L. 106–113 substituted ''one or more of subsections (e), (f), and (g)'' for ''subsection (f) or (g)''.

1995—Pub. L. 104–41 designated first and second pars. as subsecs. (a) and (c), respectively, and added subsec. (b).

1984—Pub. L. 98–622 inserted ''Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.''

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by section 3(c) of Pub. L. 112–29 effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

Amendment by section 20(j) of Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, see section 20(*l*) of Pub. L. 112–29, set out as a note under section 2 of this title.

EFFECTIVE DATE OF 2004 AMENDMENT

Pub. L. 108–453, § 3, Dec. 10, 2004, 118 Stat. 3596, provided that:

''(a) IN GENERAL.—The amendments made by this Act [amending this section] shall apply to any patent granted on or after the date of the enactment of this Act [Dec. 10, 2004].

''(b) SPECIAL RULE.—The amendments made by this Act shall not affect any final decision of a court or the United States Patent and Trademark Office rendered before the date of the enactment of this Act, and shall not affect the right of any party in any action pending before the United States Patent and Trademark Office or a court on the date of the enactment of this Act to have that party's rights determined on the basis of the provisions of title 35, United States Code, in effect on the day before the date of the enactment of this Act.''

EFFECTIVE DATE OF 1999 AMENDMENT

Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4807(b)], Nov. 29, 1999, 113 Stat. 1536, 1501A–591, provided that: ''The amendment made by this section [amending this section] shall apply to any application for patent filed on or after the date of the enactment of this Act [Nov. 29, 1999].''

EFFECTIVE DATE OF 1995 AMENDMENT

Section 3 of Pub. L. 104–41 provided that: ''The amendments made by section 1 [amending this section] shall apply to any application for patent filed on or after the date of enactment of this Act [Nov. 1, 1995] and to any application for patent pending on such date of enactment, including (in either case) an application for the reissuance of a patent.''

EFFECTIVE DATE OF 1984 AMENDMENT

Section 106 of Pub. L. 98–622 provided that:

''(a) Subject to subsections (b), (c), (d), and (e) of this section, the amendments made by this Act [probably should be ''this title'', meaning title I of Pub. L. 98–622, enacting section 157 of this title, amending this section and sections 116, 120, 135, and 271 of this title, and enacting a provision set out as a note under section 157 of this title] shall apply to all United States patents granted before, on, or after the date of enactment of this Act [Nov. 8, 1984], and to all applications for United States patents pending on or filed after the date of enactment.

''(b) The amendments made by this Act shall not affect any final decision made by the court or the Patent and Trademark Office before the date of enactment of this Act [Nov. 8, 1984], with respect to a patent or application for patent, if no appeal from such decision is pending and the time for filing an appeal has expired.

''(c) Section 271(f) of title 35, United States Code, added by section 101 of this Act shall apply only to the supplying, or causing to be supplied, of any component or components of a patented invention after the date of enactment of this Act [Nov. 8, 1984].

''(d) No United States patent granted before the date of enactment of this Act [Nov. 8, 1984] shall abridge or affect the right of any person or his successors in business who made, purchased, or used prior to such effective date anything protected by the patent, to continue the use of, or to sell to others to be used or sold, the specific thing so made, purchased, or used, if the patent claims were invalid or otherwise unenforceable on a ground obviated by section 103 or 104 of this Act [amending this section and sections 116 and 120 of this title] and the person made, purchased, or used the specific thing in reasonable reliance on such invalidity or unenforceability. If a person reasonably relied on such invalidity or unenforceability, the court before which

such matter is in question may provide for the continued manufacture, use, or sale of the thing made, purchased, or used as specified, or for the manufacture, use, or sale of which substantial preparation was made before the date of enactment of this Act, and it may also provide for the continued practice of any process practiced, or for the practice of which substantial preparation was made, prior to the date of enactment, to the extent and under such terms as the court deems equitable for the protection of investments made or business commenced before the date of enactment.

''(e) The amendments made by this Act shall not affect the right of any party in any case pending in court on the date of enactment [Nov. 8, 1984] to have their rights determined on the basis of the substantive law in effect prior to the date of enactment.''

§ 104. Invention made abroad

(a) IN GENERAL.—

(1) PROCEEDINGS.—In proceedings in the Patent and Trademark Office, in the courts, and before any other competent authority, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or other activity with respect thereto, in a foreign country other than a NAFTA country or a WTO member country, except as provided in sections 119 and 365 of this title.

(2) RIGHTS.—If an invention was made by a person, civil or military—

(A) while domiciled in the United States, and serving in any other country in connection with operations by or on behalf of the United States,

(B) while domiciled in a NAFTA country and serving in another country in connection with operations by or on behalf of that NAFTA country, or

(C) while domiciled in a WTO member country and serving in another country in connection with operations by or on behalf of that WTO member country,

that person shall be entitled to the same rights of priority in the United States with respect to such invention as if such invention had been made in the United States, that NAFTA country, or that WTO member country, as the case may be.

(3) USE OF INFORMATION.—To the extent that any information in a NAFTA country or a WTO member country concerning knowledge, use, or other activity relevant to proving or disproving a date of invention has not been made available for use in a proceeding in the Patent and Trademark Office, a court, or any other competent authority to the same extent as such information could be made available in the United States, the Director, court, or such other authority shall draw appropriate inferences, or take other action permitted by statute, rule, or regulation, in favor of the party that requested the information in the proceeding.

(b) DEFINITIONS.—As used in this section—

(1) the term ''NAFTA country'' has the meaning given that term in section 2(4) of the North American Free Trade Agreement Implementation Act; and

(2) the term ''WTO member country'' has the meaning given that term in section 2(10) of the Uruguay Round Agreements Act.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 93–596, §1, Jan. 2, 1975, 88 Stat. 1949; Pub. L. 94–131, §6, Nov. 14, 1975, 89 Stat. 691; Pub. L. 98–622, title IV, §403(a), Nov. 8, 1984, 98 Stat. 3392; Pub. L. 103–182, title III, §331, Dec. 8, 1993, 107 Stat. 2113; Pub. L. 103–465, title V, §531(a), Dec. 8, 1994, 108 Stat. 4982; Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, §13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906; (As amended Pub. L. 112–29, §20(j), Sept. 16, 2011, 125 Stat. 335.)

AMENDMENT OF SECTION

Pub. L. 112–29, §20(j), (l), Sept. 16, 2011, 125 Stat. 335, provided that, effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, this section is amended by striking ''of this title'' each place that term appears. See 2011 Amendment note below.

REPEAL OF SECTION

Pub. L. 112–29, §3(d), (n), Sept. 16, 2011, 125 Stat. 287, 293, provided that, effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, this section is repealed.

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., §109 (Aug. 8, 1946, ch. 910, 60 Stat. 943).

Language has been changed and the last sentence has been broadened to refer to persons serving in connection with operations by or on behalf of the United States, instead of solely in connection with the prosecution of the war.

REFERENCES IN TEXT

Section 2(4) of the North American Free Trade Agreement Implementation Act, referred to in subsec. (b)(1), is classified to section 3301(4) of Title 19, Customs Duties.

Section 2(10) of the Uruguay Round Agreements Act, referred to in subsec. (b)(2), is classified to section 3501(10) of Title 19.

AMENDMENTS

2011—Subsec. (a)(1). Pub. L. 112–29, 20(j), struck out ''of this title'' after ''365''.

2002—Subsec. (a)(3). Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

1999—Subsec. (a)(3). Pub. L. 106–113, as amended by Pub. L. 107–273, substituted ''Director'' for ''Commissioner''.

1994—Pub. L. 103–465 amended section generally, expanding scope of section to include WTO member countries along with NAFTA countries and defining term ''WTO member country''.

1993—Pub. L. 103–182 amended section catchline and text generally. Prior to amendment, text read as follows: ''In proceedings in the Patent and Trademark Office and in the courts, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or other activity with respect thereto, in a foreign country, except as provided in sections 119 and 365 of this title. Where an invention was made by a person, civil or military, while domiciled in the United States and serving in a foreign country in connection with operations by or on behalf of the United States, he shall be entitled to the same rights of priority with respect to such invention as if the same had been made in the United States.''

TAB 10

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, §4732(a)(10)(A)] of Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, §4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

Amendment by section 1000(a)(9) [title IV, §4801(a)] of Pub. L. 106–113 effective Nov. 29, 1999, and applicable to any provisional application filed on or after June 8, 1995, see section 1000(a)(9) [title IV, §4801(d)] of Pub. L. 106–113, set out as a note under section 119 of this title.

EFFECTIVE DATE OF 1994 AMENDMENT

Amendment by Pub. L. 103–465 effective 6 months after Dec. 8, 1994, and applicable to all patent applications filed in the United States on or after that effective date, with provisions relating to earliest filed patent application, see section 534(b)(1), (3) of Pub. L. 103–465, set out as a note under section 154 of this title.

EFFECTIVE DATE OF 1982 AMENDMENT

Amendment by Pub. L. 97–247 effective six months after Aug. 27, 1982, see section 17(c) of Pub. L. 97–247, set out as an Effective Date note under section 294 of this title.

EMERGENCY RELIEF FROM POSTAL SITUATION AFFECTING PATENT, TRADEMARK, AND OTHER FEDERAL CASES

Pub. L. 92–34, June 30, 1971, 85 Stat. 87, provided that a patent or trademark application would be considered filed in the United States Patent Office on the date that it would have been received by the Patent Office except for the delay caused by emergency situation affecting postal service from Mar. 18, 1970 to Mar. 30, 1970, if a claim was made.

§ 112. Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 89–83, §9, July 24, 1965, 79 Stat. 261; Pub. L. 94–131, §7, Nov. 14, 1975, 89 Stat. 691; Pub. L. 112–29, §4(c), Sept. 16, 2011, 125 Stat. 296.)

AMENDMENT OF SECTION

Pub. L. 112–29, §4(c), (e), Sept. 16, 2011, 125 Stat. 296, 297, provided that, effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to any patent application that is filed on or after that effective date, this section is amended:

(1) in the first undesignated paragraph—

(A) by striking ''The specification'' and inserting ''(a) IN GENERAL.—The specification''; and

(B) by striking ''of carrying out his invention'' and inserting ''or joint inventor of carrying out the invention'';

(2) in the second undesignated paragraph—

(A) by striking ''The specification'' and inserting ''(b) CONCLUSION.—The specification''; and

(B) by striking ''applicant regards as his invention'' and inserting ''inventor or a joint inventor regards as the invention'';

(3) in the third undesignated paragraph, by striking ''A claim'' and inserting ''(c) FORM.—A claim'';

(4) in the fourth undesignated paragraph, by striking ''Subject to the following paragraph,'' and inserting ''(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e),'';

(5) in the fifth undesignated paragraph, by striking ''A claim'' and inserting ''(e) REFERENCE IN MULTIPLE DEPENDENT FORM.—A claim''; and

(6) in the last undesignated paragraph, by striking ''An element'' and inserting ''(f) ELEMENT IN CLAIM FOR A COMBINATION.—An element''.

See 2011 Amendment note below.

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., §33 (R.S. 4888, amended (1) Mar. 3, 1915, ch. 94, §1, 38 Stat. 958; (2) May 23, 1930, ch. 312, §2, 46 Stat. 376).

The sentence relating to signature of the specification is omitted in view of the general requirement for a signature in section 111.

The last sentence is omitted for inclusion in the chapter relating to plant patents.

The clause relating to machines is omitted as unnecessary and the requirement for disclosing the best mode of carrying out the invention is stated as generally applicable to all types of invention (derived from Title 35, U.S.C., 1946 ed., §69, first defense).

The clause relating to the claim is made a separate paragraph to emphasize the distinction between the description and the claim or definition, and the language is modified.

A new paragraph relating to functional claims is added.

AMENDMENTS

2011—Pub. L. 112–29 designated first to sixth pars. as subsecs. (a) to (f), respectively, inserted headings, in subsec. (a), substituted ''or joint inventor of carrying

out the invention'' for ''of carrying out his invention'', in subsec. (b), substituted ''inventor or a joint inventor regards as the invention'' for ''applicant regards as his invention'', and in subsec. (d), substituted ''Subject to subsection (e),'' for ''Subject to the following paragraph,''.

1975—Pub. L. 94–131 substituted provision authorizing the writing of claims, if the nature of the case admits, in dependent or multiple dependent form for prior provision for writing claims in dependent form, required claims in dependent form to contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed, substituted text respecting construction of a claim in dependent form so as to incorporate by reference all the limitations of the claim to which it refers for prior text for construction of a dependent claim to include all the limitations of the claim incorporated by reference into the dependent claim, and inserted paragraph respecting certain requirements for claims in multiple dependent form.

1965—Pub. L. 89–83 permitted a claim to be written in independent or dependent form, and if in dependent form, required it to be construed to include all the limitations of the claim incorporated by reference into the dependent claim.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to any patent application that is filed on or after that effective date, see section 4(e) of Pub. L. 112–29, set out as a note under section 111 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

EFFECTIVE DATE OF 1965 AMENDMENT

Amendment by Pub. L. 89–83 effective three months after July 24, 1965, see section 7(a) of Pub. L. 89–83, set out as a note under section 41 of this title.

§ 113. Drawings

The applicant shall furnish a drawing where necessary for the understanding of the subject matter sought to be patented. When the nature of such subject matter admits of illustration by a drawing and the applicant has not furnished such a drawing, the Director may require its submission within a time period of not less than two months from the sending of a notice thereof. Drawings submitted after the filing date of the application may not be used (i) to overcome any insufficiency of the specification due to lack of an enabling disclosure or otherwise inadequate disclosure therein, or (ii) to supplement the original disclosure thereof for the purpose of interpretation of the scope of any claim.

(July 19, 1952, ch. 950, 66 Stat. 799; Pub. L. 94–131, § 8, Nov. 14, 1975, 89 Stat. 691; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 34, part (R.S. 4889, amended Mar. 3, 1915, ch. 94, § 2, 38 Stat. 958).

The requirement for signature in the corresponding section of existing statute is omitted; regulations of the Patent Office can take care of any substitute. A redundant clause is omitted.

AMENDMENTS

2002—Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

1999—Pub. L. 106–113, as amended by Pub. L. 107–273, substituted ''Director'' for ''Commissioner''.

1975—Pub. L. 94–131 substituted provisions respecting drawings requiring necessary-for-understanding drawings and submission of drawings within prescribed time period and limiting use of drawings submitted after filing date of application for prior provision requiring the applicant to furnish a drawing when the nature of the case admitted it.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, § 4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

§ 114. Models, specimens

The Director may require the applicant to furnish a model of convenient size to exhibit advantageously the several parts of his invention.

When the invention relates to a composition of matter, the Director may require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment.

(July 19, 1952, ch. 950, 66 Stat. 799; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 34, part (R.S. 4890 and 4891).

The change in language in the second paragraph broadens the requirement for specimens.

AMENDMENTS

2002—Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

1999—Pub. L. 106–113, as amended by Pub. L. 107–273, substituted ''Director'' for ''Commissioner'' in two places.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, § 4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

§ 115. Oath of applicant

The applicant shall make oath that he believes himself to be the original and first inventor of the process, machine, manufacture, or composition of matter, or improvement thereof, for which he solicits a patent; and shall state of what country he is a citizen. Such oath may be made before any person within the United States authorized by law to administer oaths,

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B). This brief contains 13,285 words as calculated by the "Word Count" feature of Microsoft Word 2007, the word processing program used to create it.

The undersigned further certifies that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman 14 point font.

Dated: September 9, 2013

/s/ Edward R. Reines
Edward R. Reines

Counsel for Defendants-Appellants

CERTIFICATE OF SERVICE

I hereby certify that on September 9, 2013, I filed or caused to be filed copies of the foregoing with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system and served or caused to be served a copy on all counsel of record by the CM/ECF system and electronic mail.

Dated: September 9, 2013

/s/ Edward R. Reines
Edward R. Reines

Counsel for Defendants-Appellants